Exploring enthesitis as a basis for nail disease in psoriasis and psoriatic arthritis using high resolution MRI and ultrasound

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The candidate confirms that the work submitted is her own, except where work which has formed part of jointly-authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

Chapter Two includes work from a jointly authored publication by Zoe Ash and Cecile Gaujoux-Viala. Zoe Ash performed the systematic literature and meta-analysis for biological therapies, synovectomy and glucocorticoids. Cecile Gaujoux-Viala performed the systematic literature review and data analysis for disease modifying anti-rheumatic and non-steroidal anti-inflammatory drugs. Both authors contributed equally to the writing of the paper.

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greater magnitude of underlying systemic subclinical enthesopathy than those with normal nails. Ann Rheum Dis. 2012 Apr;71(4):553-6. [1]

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Original publications

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Aydin SZ*, **Ash ZR*,** Tinazzi I, Castillo-Gallego C, Kwok C, Wilson C, Goodfield M, Gisondi P, Tan AL, Marzo-Ortega H, Emery P, Wakefield RJ, McGonagle DG. The link between enthesitis and arthritis in psoriatic arthritis: a switch to a vascular phenotype at insertions may play a role in arthritis development. Ann Rheum Dis. 2013 Jun;72(6):992-5

Aydin SZ, Castillo-Gallego C, **Ash ZR**, Marzo-Ortega H Emery P, Wakefield RJ, Wittmann M, McGonagle D. Ultrasonographic Assessment of Nail in Psoriatic Disease Shows a Link between Onychopathy and Distal Interphalangeal Joint Extensor Tendon Enthesopathy. Dermatology. 2012;225(3):231-5.

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Oral presentations

Ash ZR, Tinazzi I, Castillo-Gallego C, Kwok C, Wilson C, Goodfield M, Gisondi P, Tan AL, Marzo-Ortega H, Wakefield RJ, Emery P, Aydin S and McGonagle D. Nail Disease in Psoriasis Is Associated with Sonographically Determined Systemic Subclinical Enthesopathy. NIHR Experimental Medicine Training Camp, Ashridge, 2012.

Ash ZR, Tinazzi I, Castillo-Gallego C, Kwok C, Wilson C, Goodfield M, Gisondi P, Tan AL, Marzo-Ortega H, Wakefield RJ, Emery P, Aydin S and McGonagle D. Nail Disease in Psoriasis Is Associated with Sonographically Determined Systemic Subclinical Enthesopathy. ACR, Chicago, 2011.

Ash ZR, Tinazzi I, Castillo-Gallego C, Kwok C, Wilson C, Goodfield M, Gisondi P, Tan AL, Marzo-Ortega H, Wakefield RJ, Emery P, Aydin S and McGonagle D. Nail Disease in Psoriasis Is Associated with Sonographically Determined Systemic Subclinical Enthesopathy. Gene to Clinic, London, 2011.

Ash ZR, Hodgson R, Grainger, A, Kwok C, Wilson C, Goodfield M, Marzo-Ortega H, Tan AL, McGonagle D. Distal interphalangeal joint enthesitis adjacent to the nail matrix is present in a subgroup of patients with psoriasis without clinical arthritis. GRAPPA annual meeting, Naples, 2011.

Poster presentations

Ash ZR, Hodgson R, Grainger A, Aydin SZ, Castillo-Gallego C, Tan AL, Marzo-Ortega H, McGonagle D. Imaging of psoriatic nail disease pre and post anti-TNF therapy shows persistent subclinical inflammation despite good clinical response. GRAPPA Annual Meeting, Stockholm, 2012.

Aydin SZ*, **Ash ZR***, Tinazzi I, Castillo-Gallego C, Kwok C, Wilson C, Goodfield M, Gisondi P, Tan AL, Marzo-Ortega H, Emery P, Wakefield R, McGonagle D. The link between enthesitis and arthritis in psoriatic arthritis: a switch to a vascular phenotype at insertions may play a role in arthritis development. EULAR, Berlin, 2012.

Aydin SZ*, **Ash ZR***, Tinazzi I, Castillo-Gallego C, Kwok C, Wilson C, Goodfield M, Gisondi P, Tan AL, Marzo-Ortega H, Emery P, Wakefield R, McGonagle D. The path from psoriasis to psoriatic arthritis - a switch to a vascular phenotype at sites of subclinical enthesopathy could be relevant in the dermatological setting to predict psoriatic arthritis development. Gene to Clinic, London, 2011.

Ash ZR, Aydin S, Castillo-Gallego C, Kwok C, Wilson C, Goodfield M, Marzo-Ortega H, Tan AL, McGonagle D. Nail and entheseal ultrasound in patients with psoriasis: is subclinical enthesitis more frequent in patients with nail disease? EADV, Lisbon, 2011.

Ash ZR, Hodgson R, Grainger, A, Kwok C, Wilson C, Goodfield M, Marzo-Ortega H, Tan AL, McGonagle D. Distal interphalangeal joint enthesitis adjacent to the nail matrix is present in a subgroup of patients with psoriasis without clinical arthritis. EADV, Lisbon, 2011.

Aydin SZ*, **Ash ZR***, Tinazzi I, Castillo-Gallego C, Kwok C, Wilson C, Goodfield M, Gisondi P, Tan AL, Marzo-Ortega H, Wakefield R, Emery P, McGonagle D. The link between enthesitis and arthritis in psoriasis and psoriatic arthritis: a switch to vascular phenotype at insertions may play a role in arthritis development. GRAPPA annual meeting, Naples, 2011.

Ash ZR, Aydin S, Hodgson R, Kwok C, Wilson C, Goodfield M, Marzo-Ortega H, Tan AL, McGonagle D. Ultrasound and high resolution magnetic resonance imaging to explore nail changes and enthesitis in patients with psoriasis. GRAPPA annual meeting, Miami Beach, 2010.

Ash ZR, Hodgson R, Aydin S, Marzo-Ortega H, Tan AL, McGonagle D. High resolution magnetic resonance imaging to explore nail changes and enthesitis in patients with psoriasis. Seventh International Congress on Spondyloarthropathies, Gent, 2010.

Ash ZR, Hodgson R, Marzo-Ortega H, Tan AL, McGonagle D. High resolution magnetic resonance imaging to explore nail changes and enthesitis in patients with psoriasis. EADV, Gothenberg, 2010.

Abstract

The role of enthesitis in the pathogenesis of psoriatic arthritis has been increasingly recognised in the last twenty years. High resolution imaging techniques and histology have shown that the distal interphalangeal (DIP) joint extensor tendon is directly anchored to the nail. More recently, it has become apparent that a significant proportion of asymptomatic psoriasis patients have subclinical enthesitis at sites such as the Achilles tendon. This thesis explored the hypothesis that nail disease without clinical arthritis was associated with DIP joint enthesopathy and that nail disease equated with remote systemic enthesopathy.

Imaging studies utilising magnetic resonance imaging (MRI) of the DIP joint confirmed the relationship between enthesitis and nail disease in psoriatic arthritis, and found subtle enthesitis and osteitis in psoriasis patients. High resolution ultrasound that has an intrinsically greater resolution than MRI showed extensor tendon enthesopathy of the DIP to be common in psoriasis patients with nail disease, but not those without nail disease. It was also shown that nail disease in psoriasis patients without arthritis was associated with sonographically-determined remote enthesopathy in the lower limbs. In a small pilot study (N=9), despite clinical improvements MRI showed ongoing inflammation in and around the DIP joint after six months treatment with a TNF inhibitor.

The long term outlook of DIP joint psoriatic arthritis was studied, with a review of a cohort of patients at a mean of nine years after a baseline MRI scan. This demonstrated joint space narrowing in the majority of patients. The development of arthritis mutilans or ankylosis was seen in a minority, but without a close correlation with baseline MRI findings.

Collectively these findings show a link between nail disease in psoriasis patients and both local and systemic subclinical enthesopathy.

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Chapter 1
Introduction

The seronegative spondyloarthropathies (SpA) are a group of inflammatory arthritides which include psoriatic arthritis (PsA), ankylosing spondylitis (AS), reactive arthritis, enteropathic arthritis and undifferentiated SpA. Psoriatic arthritis was first described as a clinical entity distinct from rheumatoid arthritis (RA) by the late Professor Verna Wright in the 1950s (Wright 1978). Psoriasis is a common skin condition occurring in approximately 2% of the population (Stern et al. 2004; Gelfand et al. 2005b). Approximately 20 – 40% of psoriasis patients develop PsA and currently there is no means to predict in an individual psoriasis patient whether they will go on to develop PsA.

Recent descriptions of inflammation at ligament and tendon insertions, or enthesitis, being a primary pathology in the spondyloarthropathies has led to increased interest in understanding the disease processes. The finding of enthesitis in areas such as the Achilles tendon in psoriasis patients without arthritis or arthralgia also supports the concept that psoriasis is 'more than skin deep' – in other words that patients with psoriasis have multi-organ involvement (Scarpa et al. 2006a; Gisondi et al. 2008). This includes increased cardiovascular risk, obesity, lipid abnormalities and psychological morbidity. However, the significance of the enthesitis in patients with psoriasis is still not clear.

Historically it has been noted that nail disease is more strongly associated with PsA than psoriasis (Wright 1956). Imaging studies in PsA have shown the nail to be closely associated with the entheses of ligaments and tendons around the distal interphalangeal (DIP) joint (Tan et al. 2007). Little is known about the pathogenesis of nail disease in psoriasis patients.

Historically it has been suggested that some nail lesions may relate to psoriatic plaques in the nail bed (Zaias 1990). The recent finding that nail disease in PsA is associated with DIP joint arthritis and enthesitis raises the question as to whether the same processes are true in psoriasis. Certainly a substantial proportion of psoriasis patients report nail pain (de Jong et al. 1996), but the origin of the pain is not yet understood. Detailed imaging of these structures may allow us to understand the pathogenesis of nail disease in both PsA and psoriasis, and to study whether nail disease in psoriasis is related to local DIP joint enthesitis.

Modern treatment options for PsA include non-steroidal anti-inflammatory drugs, disease modifying drugs and TNF antagonists. These treatments are largely borrowed from rheumatoid arthritis, and primary outcomes assessed in clinical trials tend to assess articular disease. Nonetheless, efficacy has been shown in enthesitis and nail disease, both as secondary outcomes (Ash et al. 2012a). Indeed improvements in nail disease can be dramatic, and perhaps surprising when they occur in patients with severely damaged DIP joints where you might imagine the nail matrix is also damaged beyond repair.

In common with spinal and sacroiliac joint disease, DIP joint disease in PsA is associated with a diffuse pattern of bone marrow oedema (BMO) when seen on magnetic resonance imaging (MRI) (Tan et al. 2006a). This BMO has been shown at other sites such as the sacroiliac joint to represent an osteitis (Bollow et al. 2000; Marzo-Ortega et al. 2007b) and to be associated with the development of future radiographic AS (Bennett et al. 2008). It is however unknown whether osteitis in the DIP joint progresses to arthritis mutilans and whether it is also linked to nail disease.

This thesis aims to study the relationship between enthesopathy and nail disease in detail, to improve our understanding of the pathogenesis of nail disease in psoriasis patients and to assess whether nail disease might be a

clinical marker for those patients who have imaging evidence of subclinical enthesitis. Both MRI and ultrasound (US) will be used in order to study both the peripheral entheses and the microenvironment of the DIP joint.

The structure of this thesis can be summarised as follows:

Chapter Two **Review of the literature**

This chapter overviews psoriasis and psoriatic arthritis, including the epidemiology, pathogenesis and treatment of the different forms of the disease. The pathogenesis of nail disease is explored, and imaging methods and techniques used in the assessment of psoriatic disease are reviewed.

Chapter Three **Aims and objectives**

This chapter sets out the research questions and hypotheses for the thesis.

Chapter Four **Ultrasound imaging of the peripheral entheses in psoriasis patients**

In this chapter the relationship between subclinical ultrasound enthesitis and nail disease is assessed in psoriasis patients.

Chapter Five **Comparison of the ultrasound appearances of peripheral enthesitis in psoriasis and psoriatic arthritis patients and healthy controls**

The characteristics of ultrasound-determined enthesopathy are here compared between psoriasis patients, those with PsA and healthy controls.

Chapter Six **High resolution magnetic resonance imaging of the distal interphalangeal joint and nail in psoriasis and psoriatic arthritis**

Studying the DIP joint in detail, the relationship between nail disease and local enthesopathy and bone changes is explored using MRI.

Chapter Seven **Ultrasound imaging of the nail and distal interphalangeal joint and nail in psoriasis and psoriatic arthritis**

In this chapter the ability of ultrasound to assess the nail plate and matrix is assessed, in comparison to clinical assessment.

Chapter Eight **Imaging of psoriatic nail disease pre and post TNF inhibitor therapy**

The known clinical response of nail disease to TNF inhibitors is examined further, using MRI to study changes in the bone and entheses before and during treatment.

Chapter Nine **An assessment of high resolution magnetic resonance imaging of distal interphalangeal joint psoriatic arthritis for predicting radiographic joint destruction at nine years**

This chapter reviews the long term outcomes of a cohort of patients who underwent high resolution MRI for active DIPJ arthritis, assessing their radiographic progression over time.

Chapter Ten **Discussion and future directions**

The results presented in all chapters are reviewed and discussed in the context of new literature and data available. Future avenues for research are explored, in particular the prediction of which psoriasis patients will later develop psoriatic arthritis.

Chapter Eleven **Conclusions**

Chapter 2
Review of the literature

2.1 Psoriasis

2.1.1. Epidemiology

Psoriasis is a common skin disease, occurring in approximately 2% of the population (Stern et al. 2004; Gelfand et al. 2005b). Although initial clinical presentations vary, the majority of patients go on to develop chronic plaque psoriasis. The severity of psoriasis in an individual can fluctuate. Flares of psoriasis have been linked to streptococcal infections (especially guttate psoriasis), stress, hormonal changes and medications such as lithium, beta-blockers and anti-malarials (Fry 1988; Gudjonsson et al. 2007). Psoriasis is found throughout the world, with prevalence estimates ranging from 0% in Samoan and South American Indian populations, to 4.8% in Norway (a patient-reported estimate) (Gudjonsson et al. 2007). Rates for psoriasis are equal in males and females (Fry 1988). It is rare in infants, presents in most individuals between the teenage years and the age of 30 but can occur at any age (Fry 1988; Gudjonsson et al. 2007). Patients presenting at an early age with psoriasis are more likely to have severe disease, a positive family history and psoriasis-associated HLA subtypes (Gudjonsson et al. 2007).

2.1.2. Pathology

Psoriasis most commonly occurs as raised erythematous skin plaques with clearly demarcated borders and a scaly surface. The underlying pathological changes are abnormal proliferation and differentiation of keratinocytes, with T cell infiltrates in the dermis and epidermis. Within the

psoriatic plaque, superficial dermal microvessels are elongated, tortuous and widened, while uninvolved skin in the same subject does not show these changes (Hern et al. 2007).

Psoriasis is part of a disease spectrum, with several phenotypes of psoriasis being described as well as associations with a particular form of arthritis (Psoriatic Arthritis, PsA) and co-morbidities including obesity and increased cardiovascular risk. This has led to the term 'psoriatic disease' to explain the varied features that different patients may present with (Figure 1) (Scarpa et al. 2006a).

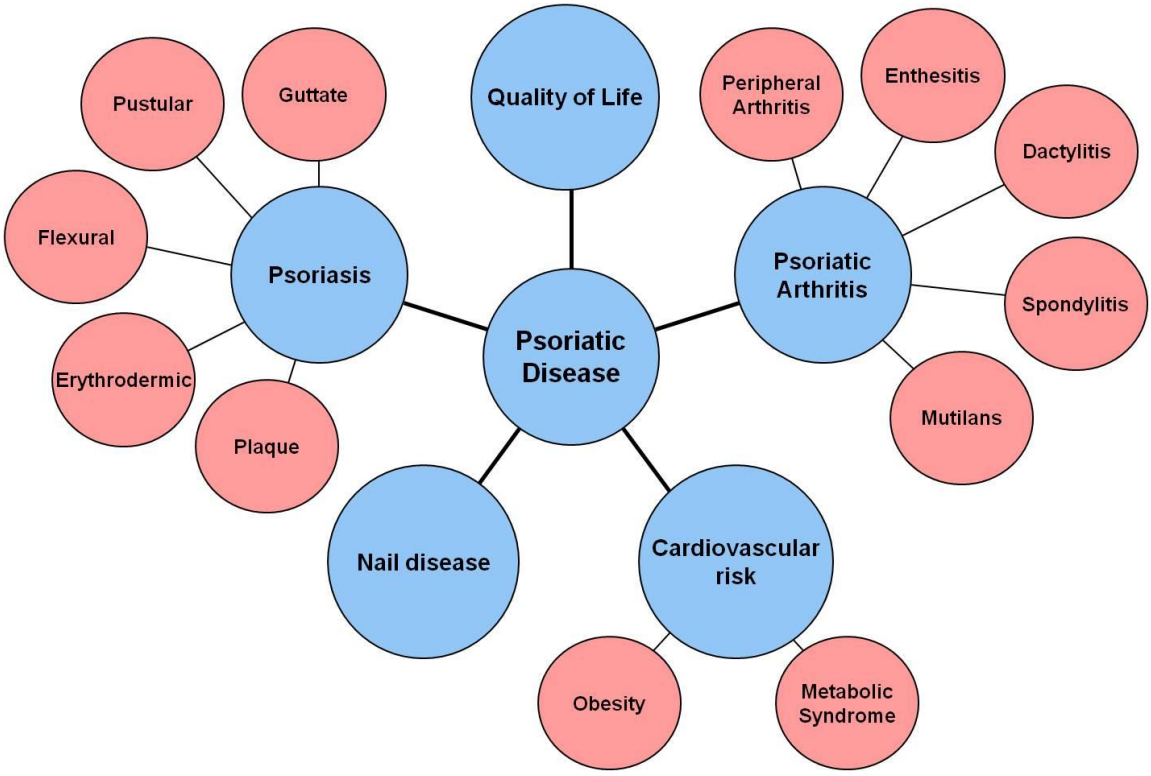


Figure 1. The spectrum of psoriatic disease

2.1.3. Burden of disease

Psoriasis may have a major impact on a patient's life, affecting their quality of life, employment and self esteem (Wu et al. 2009; Magin et al. 2010). The application of treatments also takes significant time (Devaux et al. 2012). Relationships are frequently affected, with psoriasis patients

describing a marked impact on their sexual relationships and intimacy (Magin et al. 2010). When psoriasis is severe (such as with erythroderma or widespread plaque disease) it may result in hospitalisations and severe systemic illness (Condon et al. 1994). In a Canadian study, the mean annual cost of psoriasis was $7999 per patient, with direct healthcare-associated costs accounting for 57% of this and lost productivity the remainder (Levy et al. 2012). Costs were higher in patients with more severe disease.

2.1.4. Systemic manifestations of psoriasis

Several large studies have now demonstrated a relationship between psoriasis and an increased risk of the metabolic syndrome, hypertension, hypercholesterolaemia, obesity and depression (Cohen et al. 2010; Schmitt et al. 2010; Love et al. 2011). Obesity is more prevalent in patients with psoriasis but is also noted to be present prior to the development of psoriasis as an independent risk factor (Herron et al. 2005; Setty et al. 2007; Wolk et al. 2009). There has also been demonstration of an association between body mass index and psoriasis severity, with reductions in the PASI with weight loss (Huang et al. 2010; Hossler et al. 2011). A recent study using positron emission tomography (PET) found that psoriasis patients had significant uptake not just in the musculoskeletal system but also the liver, in keeping with the known association with fatty liver disease (Miele et al. 2009; Mehta et al. 2011; Tsai et al. 2011). Psychological morbidity is common, including depression, anxiety and an increased rate of suicide (Magin et al. 2009; Kurd et al. 2010; Han et al. 2011),

2.1.5 Clinical assessment

Clinical assessment of psoriasis should take into account the phenotypic type of psoriasis (such as plaque, guttate, palmar-plantar). The distribution of lesions is important, partly because of the prognostic implications of

lesions in certain areas for the development of PsA (Wilson et al. 2009a) but also because psoriasis in body areas such as the face and genitals may have more functional and psychological impact than psoriasis in other areas.

Several tools are available for the documentation of psoriasis severity and distribution. The simplest is the Body Surface Area (BSA) which only assesses the percentage of the body surface area currently affected by psoriasis, without grading the severity of lesions. This uses the 'rule of nines' made popular in the assessment of burns (Wallace 1951). Using this method, the arms are approximately 20% of the BSA, the legs 40%, the trunk 30% and the head 10%. A simple way to assess this has been developed, where the surface of the patient's own hand (palm and fingers) is used to equate to approximately 1% of the BSA. This allows more rapid estimation of plaques. This method may however overestimate the BSA as a study has found that the size of the hand equates to between 0.51 and 0.91% of the BSA (Long et al. 1992). An international reliability exercise found moderate inter-rater reliability when assessed by both rheumatologists and dermatologists (Chandran et al. 2009). Using the BSA, the FDA defines severe psoriasis as a BSA of more than 20%.

The Psoriasis Area and Severity Index (PASI) is the most commonly used tool (Fredriksson et al. 1978). In this method, the trunk, arms, legs and scalp are each assessed. For each area, relative percentage involvement with psoriasis gives scores between 0 and 6. Severity is then assessed as erythema, induration and desquamation, each graded using a scale from 0 – 4 on a semi-quantitative basis. The scores are then calculated together, but using a weighting to account for the relative BSA of each body area. The PASI has the advantage that it is relatively rapid to calculate, thus making it a feasible tool for clinical use. It also assesses severity both in terms of the body surface area involved as well as the severity of the plaques themselves. Given the weighting of the BSA in the PASI, limitations in the accuracy of BSA involvement do also affect the PASI. The other difficulty is the accuracy at either end of the spectrum of severity. With mild psoriasis, the PASI score is less accurate and is therefore

generally not used when the BSA is less than 3%. Also, although the maximum possible score is 72, even with very severe widespread psoriasis it is unusual to score more than 40 and therefore the distribution of common scores is skewed. (Setty et al. 2007; Berth-Jones et al. 2008). The international reliability exercise performed by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) members demonstrated substantial agreement between raters for the PASI (Chandran et al. 2009). Substantial inter-rater and intra-rater reliability were also seen in a comparison study with other assessment methods (Berth-Jones et al. 2008). Using the PASI, psoriasis severity may be divided into mild disease (PASI <3), moderate (PASI 3 – 10) or severe psoriasis (PASI >10).

Given that other factors such as the location of the psoriasis plaques may impact on how severe the patient perceives their psoriasis to be, the National Psoriasis Foundation have also suggested definitions of mild, moderate and severe psoriasis which take into account the impact on the patient (Krueger et al. 2000).

A simpler scale, the physician's global assessment has also been described. Here severity is scored as 'clear', 'almost clear', 'mild', 'mild to moderate', 'moderate', 'moderate to severe' and 'severe'. This can be a more subjective measure with some raters taking severity and distribution into account and others simply scoring severity of the plaques. It is a static score; scoring current severity without reference to previous disease activity. Moderate agreement between raters was demonstrated with this tool (Berth-Jones et al. 2008). This assessment method has been recognised by the FDA.

A number of other assessment methods have been described but are not in frequent use (Mazzotti et al. 2003; Shikiar et al. 2003; Langley et al. 2004; Berth-Jones et al. 2008). One other important issue is that all of these assessment methods were developed only for the assessment of plaque psoriasis and therefore they have not been validated for the assessment of other psoriasis sub-types.

The effect of psoriasis on quality of life is most frequently assessed using the Dermatology Life Quality Index (DLQI) (Finlay et al. 1994). This was developed in Cardiff for use in all skin diseases and includes ten questions, in which raters are asked to score how much their skin problem has affected their life from ‘not at all’ to ‘very much’. This includes questions on how the skin disease restricts activities of daily life, symptoms such as itching as well embarrassment and the impact on relationships. The DLQI has been used extensively in clinical trials and is included as a criterion to assess eligibility for TNF inhibitor therapy for psoriasis in the UK. Good internal validity, construct validity, content validity and sensitivity to change have been demonstrated (Mazzotti et al. 2003; Shikiar et al. 2003). A Rasch analysis found good internal reliability in psoriasis but poor responsiveness to change in patients with mild disease (Bronsard et al. 2010). The analysis did identify some problems with the questions and response thresholds.

The Psoriasis Disability Index (PDI) was the first questionnaire designed specifically for psoriasis patients (Finlay et al. 1987). The questionnaire has subsequently been validated and used in a variety of studies (Bronsard et al. 2010). One of the limitations of this tool is that it is more focussed on symptoms, with less assessment of the quality of life. A significant floor effect and lack of sensitivity have been noted in further studies (Nijsten et al. 2005; Fernandez-Penas et al. 2012).

2.2 Psoriatic arthritis

Although an association between psoriasis and arthritis was reported in 1818 (Alibert 1818), it was Verna Wright who first described an association between a particular form of arthritis (PsA) and psoriasis (Wright 1956). The discovery that the majority of patients with PsA were negative for rheumatoid factor also cemented the distinction between PsA and RA

(Blumberg et al. 1964). Clinical and radiographic differences help to differentiate PsA from osteoarthritis (OA) and RA (Table 1).

Table 1. Clinical and radiographic differences between PsA, RA and OA

		Psoriatic Arthritis	**Rheumatoid Arthritis**	**Osteoarthritis**
Clinical features	Pattern of joint involvement	- any peripheral joints or axial skeleton - polyarticular, oligoarticular or monoarticular disease - may affect DIP joints	- symmetrical polyarthritis sparing DIP joints	- large joint disease - nodal disease predominantly affecting DIP, PIP and thumb CMC joints
	Primary pathology	- enthesitis	- synovitis	- cartilage degradation
	Extra-articular features	- psoriasis - enthesitis - dactylitis	- rheumatoid nodules - vasculitis - pulmonary involvement	- none

	Psoriatic Arthritis	**Rheumatoid Arthritis**	**Osteoarthritis**
Radiographic features	- soft tissue swelling - joint space loss - bone proliferation - distal tuft resorption - marginal erosions - "pencil-in-cup" - osteolysis - ankylosis	- soft tissue swelling - joint space narrowing - erosions (periarticular) - joint subluxation and malalignment - ulnar deviation of the fingers at the metacarpophalangeal joints - In very late RA, fusion or joint ankylosis may occur	- joint space narrowing - osteophyte formation - subchondral sclerosis - subchondral cyst formation

2.2.1 Epidemiology

Psoriatic arthritis has a prevalence of 0.1% in the general population, with a fairly equal prevalence in both sexes (Shbeeb et al. 2000; Wilson et al. 2009b). Estimates for the prevalence of PsA in patients with psoriasis vary, in part depending on the population studied but also the method used to identify PsA (Zachariae 2003; Gelfand et al. 2005a; Wilson et al. 2009b). In the majority of patients, the onset of arthritis follows the onset of psoriasis, often by many years. Approximately 20% patients have a contemporaneous onset of psoriasis and arthritis and 20% develop arthritis as the first presentation (Gladman et al. 1987b; Jones et al. 1994).

The risk of developing psoriatic arthritis has been shown to increase with the duration and the severity of the psoriasis (Gelfand et al. 2005a). The presence of nail disease, scalp psoriasis and intergluteal psoriasis are also associated with PsA (Wilson et al. 2009a), but there are still no definitive predictors in an individual patient of the risk of later development of PsA.

2.2.2 Pathology

The pathogenesis of PsA has been historically made more difficult to study because of the wide heterogeneity of clinical manifestations. It is also difficult to conceptualise a common pathogenic mechanism for a disease which may cause erosions and bone lysis in some areas, and new bone formation in others.

Psoriatic arthritis was initially presumed to be a synovial based pathology similar to RA. Evidence for an autoimmune pathogenesis suggests that inflammation is driven by T cells reacting to either skin or synovial antigens (Haroon et al. 2012). The synovium itself shows some differences from RA synovium, with similar numbers of macrophages, fibroblasts and cytokines, but significantly lower numbers of T cells (van Kuijk et al. 2006).

In the last decade however, it has been shown that enthesitis, or inflammation at insertions such as ligament or tendon attachments to bone, forms a unifying concept for PsA and the spondyloarthropathies (McGonagle et al. 1998a; McGonagle et al. 1999). Enthesitis has been demonstrated to be a common clinically hidden finding in inflamed synovial joints (McGonagle et al. 1998b). Osteitis is frequently seen adjacent to active enthesitis (McGonagle et al. 2002). An MRI study including 13 patients with PsA found diffuse inflammation extending beyond the joint capsule in nine patients, including into the surrounding soft tissues and ligaments. In one patient, the abnormalities were predominantly extra-capsular, raising the possibility for the first time that the primary area of inflammation may not be synovial (Jevtic et al. 1995). Data from an ultrasound study also suggests that PsA patients may have enthesitis in the absence of synovitis (Frediani et al. 2001). The importance of these findings was acknowledged by the development of an MRI enthesitis scoring index to define treatment responses to biological therapy with the anti-TNF drugs in both the axial and peripheral skeleton (McGonagle et al. 2000; Marzo-Ortega et al. 2005). In dactylitis, imaging has shown widespread inflammation, with flexor tenosynovitis, bone marrow oedema, synovitis and soft tissue oedema (Coates et al. 2008a).

The entheseal hypothesis suggests a biomechanical link between skin and joint disease, with inflammation localised to sites of tissue microdamage (McGonagle et al. 1999; McGonagle et al. 2000). This is supported by the fact that both mechanical problems and degenerative disease may present a similar pattern on MRI to PsA (Kiuru et al. 2005; Tan et al. 2006a; Bennett et al. 2009). Enthesis sites have also demonstrated microdamage and local inflammatory changes in healthy subjects (Benjamin et al. 2007a; McGonagle et al. 2009b; Aydin et al. 2010a). Environmental influences are important with both Moll and Wright and the Toronto cohort amongst others reporting an association between the development of arthritis and trauma (Moll et al. 1973; Eder et al. 2011b).

2.2.3 Burden of disease

Psoriatic arthritis is a heterogenous disease, but while some forms may be mild in their disease course, other patients will develop marked deformities and disability. One prospective study found that 20% of patients developed joint damage and disability over time (Gladman et al. 1987b). In patients with at least 5 year follow-up data available, the proportion of patients with at least 5 damaged joints increased from 19% to 41% (Gladman et al. 1990). A separate prospective study involving 180 patients found that 57% of patients had erosive disease on radiographs (Torre Alonso et al. 1991). In a comparison of 47 RA and PsA patients matched for disease duration, although greater levels of peripheral joint damage were seen in RA, the levels of functional disability and quality of life were the same in the two diseases (Sokoll et al. 2001). Significant loss of productivity is seen, relating to sick leave, reduced working hours and time on benefits (Kvamme et al. 2012).

2.2.4 Genetics

A detailed review of the genetics of psoriasis and PsA is beyond the scope of this thesis. However, recent advances in genetic knowledge do shed some light on the role of the immune system in the development of PsA. The major histocompatibility complex (MHC) has been implicated most strongly, in particular HLA-Cw6 and the HLA-Cw*0602 allele. This is associated with early onset psoriasis (Allen et al. 2005; Nair et al. 2006; Queiro et al. 2012b). It is less associated with PsA than with psoriasis (Ho et al. 2007; Ho et al. 2008) and Cw6 negative patients are more likely to have scalp and nail psoriasis (Gudjonsson et al. 2002; Fan et al. 2007). Multiple genes in the IL23 pathway (thus with a role in the adaptive immune system) have been identified as being associated with PsA and psoriasis (Cargill et al. 2007). IL12B has also been implicated (Liu et al. 2008). A further GWAS study confirmed these associations as well as finding new associations within the NFκB pathway (TNF-α induced protein 3 (TNFAIP3)

and TNFAIP3 interacting protein 1 (TNIP1)) which are associated with general autoimmunity and the innate immune response (Nair et al. 2009). Within psoriasis patients, additional genes have been identified with a role in the barrier function of the skin (LCE3B and LCE3C) (Filer et al. 2008). Although there is clearly significant overlap in the genetics of psoriasis and PsA, some differences have been shown. A higher rate of HLA B27 carriage is seen in PsA patients with axial disease and of B38 and B39 in those with peripheral arthritis (Duffin et al. 2008). IL13 also appears more strongly related to PsA than psoriasis (Bowes et al. 2011; Eder et al. 2011a). Despite these advances, the major part of the heritability of psoriatic disease is still unexplained.

2.2.5 Diagnosis and classification

The diagnosis of PsA is a clinical one, based on history, examination and the phenotype of disease. To aid in research by producing a homogeneous population for study, a number of classification criteria have been developed. The first of these were the Moll and Wright criteria, which have now largely been superseded by the ClASsification of Psoriatic ARthritis (CASPAR) criteria. A number of other criteria have been proposed but not reached widespread use.

The Moll and Wright criteria are simple and quick to use – requiring just three items; the presence of psoriasis, the finding of an inflammatory arthritis and (usually) a negative rheumatoid factor (Moll et al. 1973). These were probably developed more as diagnostic criteria. The term inflammatory arthritis was deliberately broad, in order to encompass spinal disease. Moll and Wright recognised that a proportion of patients may present with what phenotypically appears to be PsA, but have a positive rheumatoid factor and therefore a negative rheumatoid factor was not an absolute requirement. This may however allow RA patients with co-existent psoriasis to be classified as PsA. These criteria are fairly broad, and do not include some particular features of PsA such as dactylitis which

may be useful in identifying patients and improving specificity. One limitation of the Moll and Wright criteria is that skin psoriasis is an absolute requirement, but there is a proportion of patients who may either develop psoriasis later, or never have psoriasis. The sensitivity in early PsA has also been shown to be lower than with the CASPAR criteria (Coates et al. 2012).

A modification of the Moll and Wright criteria was proposed by Gladman, largely to reduce the likelihood of RA patients with co-existent psoriasis being included. This involved the addition of a number of exclusion criteria suggestive of RA (Gladman et al. 1987a). Other criteria have been described by Bennett, Vasey and Espinoza, McGonagle, ESSG and Fournié (Bennett 1979; Vasey et al. 1984; Dougados et al. 1991; Fournié et al. 1999; McGonagle et al. 1999). These criteria have not been widely used or validated, although during the development process of the CASPAR criteria, a comparison was made of these existing criteria in cohorts of RA and PsA patients (Taylor et al. 2004b). This found that the most feasible and accurate were the Gladman modification of the Moll and Wright, the Vasey and Espinoza and the McGonagle criteria.

The CASPAR criteria were developed by an international group of experts (Table 2) (Taylor et al. 2006). The development process commenced with the recruitment of cohorts in a number of centres, each recruiting both cases (physician diagnosis) and controls. The controls were recruited on the basis of having another form of inflammatory arthritis, and at least half of the controls were required to have RA. Both patients and controls underwent a detailed clinical and laboratory assessment. New classification criteria were derived using Classification and Regression Trees (CART) analysis to find the most discriminant items and the addition of some items found to be independently predictive using logistic regression. In the initial analysis the sensitivity was 91.4% with a specificity of 98.7%. With these criteria, it is now possible to be classified as having PsA in the absence of skin psoriasis, also in the presence of a positive rheumatoid factor if enough other criteria are satisfied.

Table 2. The CASPAR criteria

(Taylor et al. 2006)

Inflammatory articular disease (joint, spine or entheseal) **(mandatory)**	
Plus, 3 or more points from the following:	
Evidence of current psoriasis, a personal history of psoriasis or a family history of psoriasis - Current psoriasis is defined as psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist - A personal history of psoriasis is defined as a history of psoriasis that may be obtained from a patient, family physician, dermatologist, rheumatologist, or other qualified health care provider - A family history of psoriasis is defined as a history of psoriasis in a first or second degree relative according to the patient report	Score 2 Score 1 Score 1
Typical psoriatic nail dystrophy including onycholysis, pitting and hyperkeratosis observed on current physical examination	Score 1
A negative test for the presence of rheumatoid factor by any method except latex but preferably by enzyme-linked immunosorbent assay or nephelometry, according to the local laboratory reference range	Score 1
Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist	Score 1
Radiographic evidence of juxta-articular new bone formation, appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot	Score 1

The CASPAR criteria have subsequently been validated in a number of other settings. In a Chinese cohort of PsA and other arthritis patients the

sensitivity was 98.2% and the specificity was 99.5% (Leung et al. 2010). A retrospective analysis of an existing research cohort found the criteria to be feasible to apply, with a sensitivity of 99.7% and a specificity of 99.1% (Tillett et al. 2012a). In a family medicine clinic in Toronto, the sensitivity was 100% with a specificity of 98.8 (Chandran et al. 2008).

A significant problem with the CASPAR criteria is the initial stem which requires the assessor to be confident of the finding of inflammatory articular disease. This is very difficult to define further, although the GRAPPA group are working on this (Garg et al. 2012). It makes it more difficult for non-rheumatologists (such as dermatologists) to use the criteria as they may find this assessment difficult.

One other concern was that the mean duration of disease in the initial cohort was 12.5 years and thus the criteria may not perform as well in early disease, but in fact the sensitivity of the criteria was 99.1% in an early disease cohort (mean disease duration of 1.1 year) in a tertiary care centre (Chandran et al. 2007). As this was a tertiary care centre this may be an over-estimation. A further validation in an early arthritis cohort (<24 months disease duration) found a sensitivity of 87.4% and a specificity of 99.1%. In the Leiden early arthritis clinic, the sensitivity of the CASPAR criteria was 88.7%, with a specificity of 95.6%.

In addition to the criteria developed for PsA itself, as PsA is one of the spondyloarthropathies patients may be classified using the ASAS peripheral SpA classification criteria (Rudwaleit et al. 2011). Patients would meet these criteria in the presence of arthritis, enthesitis or dactylitis along with at least one or two other SpA features. The disadvantage of using these criteria in PsA research is that the cohort identified will be more heterogeneous and may include patients with reactive arthritis or inflammatory bowel disease-associated arthritis.

2.2.6 Subtypes of psoriatic arthritis

In the original descriptions of psoriatic arthritis by Moll and Wright, a number of subtypes of disease were described (Moll et al. 1973). The five subgroups described are:

- DIP predominant arthritis
- Arthritis mutilans (with or without sacroiliitis)
- Symmetrical polyarthritis similar to RA but without a positive rheumatoid factor
- Asymmetrical oligoarthritis
- Axial disease-predominant

There is ongoing discussion as to whether these are in fact separate entities or a spectrum of manifestations and this may become clearer with further research, with full examination (clinical, laboratory, imaging, genetics) of cohorts of patients. Moll and Wright did emphasize in the original description that there may be no clear division between the subgroups.

Oligoarthritis may be more common in early PsA and some groups have described progression from one subgroup to another over the course of disease, in particular oligoarthritis to polyarthritis (Gladman et al. 1987a; Helliwell et al. 1991; Jones et al. 1994; Marsal et al. 1999; Khan et al. 2003; Veerapen 2007). The largest subgroup is generally polyarthritis, although this may be as it is more readily identified and thus diagnosed (Haroon et al. 2013), or this may be because in most cohorts, patients have established disease rather than early arthritis. This is in contrast to the original description by Moll, where only 15% had polyarticular disease, but has been a consistent finding in more recent reports. In the Toronto cohort, an association was noted between DIP disease and dactylitis, and between radiographic damage and DIP disease or polyarthritis (Gladman et al. 1987a).

2.2.7 Clinical assessment – joint counts, enthesitis, clinical assessment, dactylitis

The majority of tools for the assessment of PsA were developed for use in RA and some although in common use have not been validated for the assessment of PsA. In this section, available tools will be described and compared, along with their development and validation as appropriate.

The assessment of the peripheral joints is performed by assessing for swelling and / or tenderness of each joint in turn. In PsA, the most common joint count is the 68 tender and 66 swollen (this includes the DIP joints and assesses the hips for tenderness only). The 28 joint count used in RA is not ideal in PsA as it may underestimate disease, in particular oligoarthritis and arthritis affecting the lower limbs (Fransen et al. 2006).

A reliability exercise involving both dermatologists and rheumatologists found the overall ICC for the tender joint count to be 0.78 (substantial agreement) and for the swollen joint count 0.24 (fair agreement) (Chandran et al. 2009). There was better agreement amongst rheumatologists for the swollen joint count (ICC 0.42) than dermatologists (ICC 0.31). A separate reliability exercise found an ICC of 0.78 for the tender joint count and 0.50 for the swollen joint count (Gladman et al. 2007a). In clinical trials, joint assessments are frequently performed by other members of the multi-disciplinary team and an assessment of reliability here has again shown poor reliability, particularly amongst inexperienced raters (Tillett et al. 2012b). Responsiveness to change has been demonstrated in a number of clinical trials.

Although there are differences in the axial disease seen in PsA compared to AS, the majority of measures used to assess axial disease in clinical practice were developed for AS. The tools most frequently used are the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), the Bath Ankylosing Spondylitis Functional Index (BASFI) and the Bath Ankylosing Spondylitis Metrology Index (BASMI) (Calin et al. 1994; Garrett et al. 1994;

Jenkinson et al. 1994). The BASDAI is a six point questionnaire for completion by patients and assesses pain and stiffness. It has been tested in PsA and although it correlates well to patient-reported disease state, it does not differentiate well between axial disease and peripheral disease (Taylor et al. 2004a). The BASFI is a ten point self-completed questionnaire and assesses function. It has also been reported to correlate well to patient-reported outcomes but not differentiate well between spinal disease and peripheral arthritis (Leung et al. 2008). Other measures of function may therefore be preferred. The BASMI is a tool composed of a number of measurements of spinal mobility, which are then compared against expected values to create a score. Some of the measurements in the BASMI have demonstrated excellent inter-observer agreement while others show poor agreement (Gladman et al. 2004).

Enthesitis (inflammation at insertions such as ligament or tendon attachments to bone) is a characteristic feature of the spondyloarthropathies. It is assessed clinically by noting tenderness or swelling at the enthesis. A number of different scoring systems incorporating variable number of enthesis sites have been described. The majority of these scoring systems were developed primarily for AS patients but have since been used in PsA. The commonly used scores will be reviewed here (see also Table 3).

The first enthesitis scoring system was described by Mander in 1987 (Mander et al. 1987). This was developed in AS patients and initially assessed both sites known to be frequently involved in AS but also potential other sites. In a pilot assessment in six AS patients, sites that were not tender in any patient at any timepoint were discounted. This left 66 sites in the Mander Enthesitis Index (MEI). Some of these sites were grouped and the highest score taken forward. This included the nuchal crests, costochondral joints and the cervical, thoracic and lumbar spinous processes. Each enthesis was graded for the degree of tenderness from 0 (non tender) to 3 (wince or withdraw), giving a total score of 90. The index was then tested by one observer on one cohort of patients and compared

to other existing methods of disease activity assessment, and on another cohort of patients with weekly assessments on and off medication by three observers. The index took three minutes to complete per person in the original study. A correlation was seen between pain and stiffness scores and the MEI and it appeared sensitive to change in therapy. The principal limitation of the MEI is the complexity in terms of both number of sites to assess and the grading of the degree of tenderness, which may be subjective.

The Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) was developed as part of a simplification process from the MEI (Heuft-Dorenbosch et al. 2003). Data from the OASIS cohort was used, in which an enthesitis assessment was performed using the MEI. An analysis was performed to find the enthesis sites most frequently recorded as being tender (reduced MEI), and then enthesis sites were excluded if they were difficult to localise or neighboured other sites already included (concise index). Both of these indices were then also calculated using a dichotomous result for tenderness in place of the semi-quantitative scale. Further analysis found the concise index without grading of tenderness to perform the best and this was termed the MASES index. The INSPIRE study found moderate agreement between assessors (ICC 0.56) with better performance in AS than PsA patients (Gladman et al. 2007a). A comparative study using ultrasound in AS patients has shown a correlation between the MASES and both the total sonographic score and the sonographic score for acute enthesitis (Hamdi et al. 2011). One limitation of the MASES is a floor effect due to the reduced number of sites assessed and thus it may miss patients with low level enthesitis elsewhere.

The development of the Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis index proceeded along different lines, being based on sites noted in ultrasound and MRI studies to be common sites for enthesitis (Maksymowych et al. 2009). This literature suggested 8 possible sites, each assessed bilaterally: the greater trochanter, quadriceps tendon insertion into the patella, patellar ligament insertion into the patella and tibial tuberosity, Achilles tendon insertion, plantar fascia insertion, medial

and lateral epicondyles and the supraspinatus insertion. Tenderness was assessed as present or absent. Validation of the index was performed on two cohorts of AS patients in Canada, to assess its performance against the OMERACT filter criteria of trust, discrimination and feasibility. This confirmed the SPARCC index to be feasible and with reasonable reliability in AS patients. The INSPIRE study found excellent agreement between assessors, with an ICC of 0.81 (Gladman et al. 2007a). In AS patients, a correlation has been demonstrated between the SPARCC enthesitis index and the total sonographic enthesitis score (Hamdi et al. 2011).

The Major enthesitis index was derived for use in AS clinical trials (Braun et al. 2002) and includes 12 entheseal sites. Substantial agreement (ICC 0.70) was seen between observers when assessing PsA patients in the INSPIRE study (Gladman et al. 2007a).

The Gladman Index was described by a group from SPARCC in ten patients with PsA, using enthesis sites included in the MASES (Gladman et al. 2004). These were the rotator cuff insertion at the shoulder, tibial tuberosity at the knee, Achilles tendon, and plantar fascia insertions in the calcaneus. Fair to moderate reliability between ten assessors was demonstrated, with good agreement at the plantar fascia and tibial tuberosity. A large effect size has been seen with treatment (Healy et al. 2008b).

The Leeds Enthesitis Index (LEI) was developed specifically for use in PsA (Healy et al. 2008b). It was developed in a cohort of PsA patients with active disease (including enthesitis) who were embarking on a new therapy. A clinical assessment was recorded at each time point, including the existing enthesitis indices. An iterative process of data reduction was performed, to find the entheses which were noted to be tender the most frequently. At each step, patients who had reported that enthesis as tender were excluded, until 80% patients were accounted for. The corresponding contralateral entheses were also included in the index. This gave a simple enthesitis index of just six sites and thus is the quickest measure to use. Data from the cohort showed significant change from baseline with treatment with a good effect size, and a minimal floor effect.

It correlated well with other disease activity measures. A validation study using ultrasound found a poor relationship between clinical and ultrasound findings at sites included in the LEI, with 26% sites having US evidence of inflammation but no clinical tenderness, and 20% sites having a normal ultrasound but clinical tenderness (Ibrahim et al. 2010). The INSPIRE study found excellent agreement between assessors, with an ICC of 0.81 (Gladman et al. 2007a).

Validation of these scores is difficult because of the necessity of showing ‘truth’ without a gold standard for confirming the presence of enthesitis. The correlation between clinical enthesitis and imaging enthesitis is still debated and biopsy, while this would confirm the presence of inflammation, is not considered feasible by patients or clinicians. There is still no consensus as to the best method to be used for assessment. The LEI has the advantage of being simple and quick, as well as having been developed specifically for PsA, but may miss enthesitis in other areas.

Table 3. Enthesitis indices

Enthesitis index	**Reference**	**Number of sites**	**Sites assessed**	**Validated in PsA?**
MEI	(Mander et al. 1987)	66	Nuchal crests, manubriosternal joint, costochondral joints, greater tuberosity and medial and lateral epicondyles of the humerus, iliac crests, anterior superior iliac spines, greater trochanter, medial and lateral femur condyles, Achilles tendon and plantar fascia calcaneal insertion, cervical, thoracic, and lumbar spinous processes, ischial tuberosities, posterior superior iliac spines	No
MASES	(Heuft-Dorenbosch et al. 2003)	13	1st costochondral joint, 7th costochondral joint, posterior superior iliac spine, anterior superior iliac spines, iliac crest, 5th lumbar spinous process, proximal insertion of Achilles tendon	No
SPARCC	(Maksymowych et al. 2009)	16	Greater trochanter, quadriceps tendon insertion into the patella, patellar ligament insertion into the patella and tibial tuberosity, Achilles tendon insertion, plantar fascia insertion, medial and lateral epicondyles and the supraspinatus insertion	No

Enthesitis index	Reference	Number of sites	Sites assessed	Validated in PsA?
Major	(Braun et al. 2002)	12	Femur medial and lateral epicondyles, iliac crests, greater trochanter, calcaneal insertion of Achilles tendon, calcaneal insertion of plantar fascia	No
Gladman	(Gladman et al. 2004)	8	Rotator cuff insertion at the shoulder, tibial tuberosity at the knee, Achilles tendon, and plantar fascia insertions in the calcaneus	Yes
LEI	(Healy et al. 2008b)	6	Lateral epicondyle, medial femoral condyle, Achilles tendon insertion	Yes

Dactylitis is described as a ‘sausage’ finger or toe, where swelling of the whole digit occurs. This has been shown on imaging to include inflammation and swelling within the joints, tendon sheaths, as well as other soft tissues and skin (Coates et al. 2008a). It may be assessed simply by the number of dactylitic digits, and these may also be rated as swollen and tender (thought to represent the more acute phase) or as simply swollen, which may represent the more chronic phase. A reliability exercise using clinicians with an interest in PsA found a moderate agreement between assessors for a simple dactylitis count (reliability coefficient 0.57) (Gladman et al. 2004) and this has been used as an outcome measure in clinical trials. However, data from another reliability exercise show that while rheumatologists with an interest in PsA demonstrate substantial agreement (ICC 0.69), dermatologists with an interest in psoriasis showed no agreement (ICC 0.08) and thus experience or training may be needed for this measure to perform well (Chandran et al. 2009).

The only objective measure of dactylitis uses the Leeds dactylometer. Using this, the presence of dactylitis may be confirmed by demonstrating at least a 10% difference between the circumference of a dactylitic digit compared to the corresponding digit on the other hand or foot (Helliwell et al. 2005). The Leeds Dactylitis Index (LDI) uses the dactylometer to measure the circumference of the dactylitic digit and the corresponding contralateral digit (or the use of a normative value if that digit was also dactylitic) and then this is calculated together with a subjective semi-quantitative score for tenderness (Helliwell et al. 2005). As part of the development process for the LDI, it was demonstrated that inexperienced observers had poor inter- and intra-observer agreement in judging the subjective presence of both tender and non-tender dactylitis (without using the dactylometer). A reliability exercise of the LDI in 20 patients found an ICC of 0.70, showing substantial agreement (Gladman et al. 2007a). In a cohort of patients changing treatment, both the LDI and the LDI basic (tenderness scored simply as present or absent) performed well, with an

effect size of 0.99 and 0.90 respectively (Healy et al. 2007). Limitations of the LDI are the time involved and the requirement of a dactylometer.

The assessment of nail disease will be reviewed in section 2.5.4.

While all of these assessments are important, patient reported outcomes such as visual analogue scales are also relevant and these may give a better understanding of the impact of disease on the patient. Physicians may also under-estimate the severity of disease when compared to patient assessments (Dandorfer et al. 2012).

2.2.8 Screening for psoriatic arthritis in psoriasis patients

Given that the majority of PsA patients develop psoriasis first, and then the arthritis a number of years later, many patients are under the care of dermatologists or general practitioners at the time of development of PsA. It is clear that a significant proportion of psoriasis patients, whether under secondary care dermatology or not, have undiagnosed psoriatic arthritis (Khraishi et al. 2012; Haroon et al. 2013). This may be because the patient has not reported their symptoms to the physician, or because their symptoms were attributed to other causes. Various screening tools have been developed in the last few years to assist other physicians caring for psoriasis patients to identify PsA better. While a rheumatologist assessing every psoriasis patient would be a theoretical option for screening, in practice this is rarely possible. Screening tools are therefore useful to sub-select patients with a higher risk of PsA for review by a rheumatologist. These include the Psoriatic and Arthritic Questionnaire (PAQ), the Psoriasis Epidemiology Screening Tool (PEST), the Psoriatic Arthritis Screening and Evaluation tool (PASE), the Toronto Psoriatic Arthritis Screen (ToPAS) and the Early ARthritis for Psoriatic patients questionnaire (EARP).

The PAQ was originally developed in Canada as a twelve item questionnaire but published only in abstract form, and was subsequently studied in Sweden as a ten item questionnaire, modifying it to make it more applicable to a community cohort (Alenius et al. 2002b). This was administered to 202 community and hospital based patients with psoriasis. A ROC analysis found a score of four or greater to be the best cut-off, with a sensitivity of 60% and a specificity of 62%.

The PEST questionnaire was developed in Yorkshire from a cohort of patients with psoriasis in the community (Ibrahim et al. 2009). Patients identified by their general practitioner as having psoriasis were invited to complete a questionnaire, and a sample of those underwent a clinical assessment at the rheumatology clinic. The questionnaire was also completed by a cohort of patients with PsA. This questionnaire included items from the PAQ as well as additional questions. A manikin was also included for patients to label joints which had caused discomfort. 168 patients returned a questionnaire by post and of these, 89 were examined. A logistic regression analysis was used to reduce the questionnaire to the five best performing questions. In this initial cohort, with a cut-off score of ≥3 the sensitivity was 92% and the specificity was 78%. The advantage of the PEST questionnaire is that it is simple and short and hence requires less time to complete. A recent hospital-based study however found a much lower sensitivity of 27.5% and a specificity of 98% amongst dermatology patients with psoriasis, and a sensitivity of 86% amongst PsA patients (Haroon et al. 2013). A significant proportion of psoriasis patients were on treatments which may suppress arthritis, but perhaps more importantly the PEST questionnaire performed well in polyarticular PsA patients but poorly in other subtypes of PsA.

The PASE questionnaire was developed in the United States by a group of rheumatologists and dermatologists, using a Delphi method (Husni et al. 2007). It is a self-administered questionnaire with 15 questions. This includes two sections, one assessing function and one assessing symptoms. Each item is scored on a scale from 1 (strongly disagree) to 5 (strongly agree). This gives a maximum possible function score of 40 and

symptom score of 35, leading to a total score which can be between 15 and 75. This was then validated in 69 tertiary referral psoriasis patients, comparing the results against the gold standard of physician diagnosis for psoriasis and for psoriatic arthritis, by a dermatologist and a rheumatologist correspondingly. The PsA diagnosis took into account the Moll and Wright criteria. Osteoarthritis was also present in 35% of the patients. Psoriatic arthritis was diagnosed in 25% of the patients. Using a cut-off PASE score of 47 gave a sensitivity of 82% and a specificity of 73% for the diagnosis of PsA. Further validation was performed in 194 patients with psoriasis or PsA, with or without other rheumatic diseases such as osteoarthritis (Dominguez et al. 2009). This included analyses for the test-re-test reliability and the sensitivity to change with a change in treatment. In this group the optimal cut-off score was 44, which gave a sensitivity and specificity each of 76%. The Intraclass Correlation Coefficient (ICC) for the total PASE score was 0.90, indicating acceptable reliability. Another sub-group analysis found reasonable sensitivity to a change in disease state. Given that this questionnaire (unlike the others) assesses symptoms and function, in patients with fluctuating symptoms it may be less sensitive.

The ToPAS questionnaire was developed and validated by the group in Toronto (Gladman et al. 2009). The twelve questions were devised by an expert group of rheumatologists and dermatologists, based on features that they considered to be seen frequently in PsA patients. After initial testing for ease of use, it was shown to differentiate well between PsA patients and those with other rheumatic diseases. Subsequently the questionnaire was validated on PsA patients, patients in a tertiary care psoriasis clinic, patients from a general rheumatology clinic (with those with PsA excluded), patients from a general dermatology clinic and also a family medicine clinic. A total of 688 patients completed the questionnaires. This is a wider range of patient populations than has been studied with the other questionnaires. After completing the questionnaire all patients were assessed by a rheumatologist to confirm or refute a diagnosis of PsA. Logistic regression and receiver operating curves (ROC) were used to assess the responses to the questionnaire. A sensitivity of 89 – 93% and a specificity of 86 –

100% were seen in the different patient populations. The advantages of the ToPAS are that it has been validated in a variety of settings rather than psoriasis patients alone, and that it includes images to help patients more reliably answer the question as to whether they have psoriasis. While the PASE asks regarding current symptoms, the ToPAS assessed any history of symptoms to better classify patients who may have had intermittent symptoms. There is also no assessment of function in the ToPAS as it was designed primarily for case identification.

The EARP was designed by a group in Verona for use in patients with early psoriasis, with the aim of being simple and quick to use (Tinazzi et al. 2012). The questionnaire may be self-administered and includes ten questions. Initial validation in a cohort of 228 patients demonstrated a sensitivity of 85.2% and a specificity of 91.6%. It has not yet been widely used.

2.3 Imaging in psoriatic arthritis

A number of imaging modalities have been used in PsA. These include radiographs, ultrasound, MRI, CT, PET and bone scintigraphy. In this section, the commonly used modalities will be reviewed, including typical features seen and the advantages and disadvantages of each method. The imaging of enthesitis will be covered separately in section 2.4.1.

2.3.1 Radiographs in psoriatic arthritis

Radiographs have historically been used to assess for joint damage in PsA, among other arthritides. They are quick to perform, are easy to score as part of multicentre studies, and are acceptable to patients. Radiographs do involve a small dose of radiation, less so for radiographs of the hands and feet but a significant dose is involved in a lumbar spine film, for

example. They only give information as to bony changes (which may take some time to develop) or significant soft tissue swelling but are not able to assess soft tissues such as tendons or ligaments, or assess for current inflammation.

The typical radiographic features seen in PsA were described by Verna Wright in 1961 and have subsequently been described further in other cohorts (Wright 1961). In the peripheral joints these features include some consistent with bone proliferation (bony ankylosis, juxta-articular bone proliferation, periostitis and spur formation) and others suggestive of bone destruction (erosions, joint osteolysis, pencil-in-cup, tuft osteolysis). In the axial skeleton, syndesmophytes and sacroilitis may be seen. Plain film evidence of enthesopathy is relatively rare, and in one study was seen no more frequently in PsA than it was in RA (Helliwell et al. 2007). This may reflect that the enthesis structure is largely soft tissue which is not visualised on radiographs, and thus only severe or chronic disease may be seen.

Radiographs may be useful to differentiate between different forms of arthritis, according to the pattern of joints involved and the types of abnormality seen. Juxta-articular bony proliferation may be particularly discriminative and is included in the CASPAR criteria for this reason, although it is only seen in around 50% PsA patients (Taylor et al. 2006; Ichikawa et al. 2012).

Radiographs have been used in the majority of the trials of anti-TNF medications in PsA, showing substantial reductions in radiographic progression with these medications (Kavanaugh et al. 2006; Mease et al. 2006b; Gladman et al. 2007b; van der Heijde et al. 2007). Scoring systems for the peripheral joints have been well described, the majority of which were originally designed for the assessment of RA (Table 4).

The modified Steinbrocker score was devised in Toronto to provide more detail than in the original Steinbrocker (which merely recorded the score for the worst joint) (Rahman et al. 1998b). This method includes the DIPs, PIPs, MCPs, wrists, MTPs and great toe IPJs. Each joint is scored on a 0-4

scale, from normal to soft tissue swelling, erosion and complete joint destruction. Validation was performed on a set of films from 68 PsA patients, with x-rays taken at least two years apart. This showed excellent interobserver reliability, with an ICC of 0.86 and similar responsiveness to change when compared to the modified Larsen score. This scoring method has not been used in RCTs but has been used for radiographic scoring in a number of publications on the Toronto PsA cohort (Abu-Shakra et al. 1995; Rahman et al. 1998a).

The modified Larsen method (for PsA) includes the MCPs, PIPs, DIPs, wrists, MTPs and the 1st MTP and IPJ (Rahman et al. 1998b). Each joint is graded from 0 – 5, again ranging from normal, through degrees of erosion to total joint destruction. The final score is the mean of each individual joint score. Validation was performed in the same exercise as the modified Steinbrocker on a set of films from 68 PsA patients, with x-rays taken at least two years apart. This found excellent inter-observer reliability with an ICC of 0.87.

The PsA modified Sharp score was devised from the original Sharp score (Sharp et al. 1985) in order to monitor radiographic progression in a number of clinical trials of TNF inhibitors in PsA (Mease et al. 2004). This included a larger number of joints than the other methods, with a detailed scoring system of erosions and joint space narrowing, with a number of other PsA-specific features also recorded. Erosions were scored from 0 – 5 but with additional scores of 6 or 7 recorded if present but not added to the total score (for pencil-in-cup and gross osteolysis). Joint space narrowing was scored from 0 - 4 with widening recorded separately. Additional note was made of shaft periostitis, juxta-articular periostitis, periostitis in the wrist, and tuft resorption. In the original study inter-reader ICC values were between 0.81 and 0.88.

Another modification of the Sharp score for PsA patients was described by van der Heijde (van der Heijde 2000). The DIP joints of the hands are assessed in addition to those assessed in the original Sharp scoring system. Again a large number of joints are assessed. Erosions are scored per joint with a maximum erosion score of 5 in the hands and 10 in the feet.

Joint space narrowing is scored from 0-4, with a score of 4 representing bony ankylosis. Pencil-in-cup and gross osteolysis are scored separately, but if present that joint would score maximum for both erosions and joint space narrowing. This score has been used in a number of RCTs, showing moderate to excellent agreement between readers (Kavanaugh et al. 2006; Kavanaugh et al. 2012b).

The Ratingen score was developed for use in PsA (Wassenberg et al. 2001). It requires radiographs of the hands (including the wrist) and the feet and scores a total of 40 joints. Joints included are 8 DIPs, 2 IPJ of the thumb, 8 PIPs, 10 MCPs, 2 wrists, 2 IPJs of the great toe and the 2^{nd} to 5^{th} MTPs. Each joint is scored for destruction (scored from 0-5) and proliferation (scored from 0-4). Initial validation was performed on 20 PsA patients, each with radiographs from baseline and an average of three years. Sets of radiographs were scored in chronological order by two readers and good reliability was shown, with a minimum detectable change of around 5% of the total score.

Table 4. Radiographic scoring methods in PsA

Scoring system	Reference	Total joints	Joints included	Maximum total score	Aspects measured
Modified Steinbrocker	(Rahman et al. 1998b)	40	Each DIP, PIP, MCP and wrist, MTPs and 1st IPJ of great toe	160	Soft tissue swelling, erosion, joint destruction (in a single score)
Modified Larsen	(Rahman et al. 1998b)	32	MCPs, PIPs, DIPs, wrists and the 1st MTP and IPJ	5	Soft tissue swelling, erosion, joint destruction (in a single score)
Ratingen	(Wassenberg et al. 2001)	40	DIPs, PIPs, MCPs, wrists, IPJ thumb and great toe, MTPs	360	Destruction and proliferation

Scoring system	Reference	Total joints	Joints included	Maximum total score	Aspects measured
PsA modified Sharp	(Mease et al. 2004)	54 for erosions 50 for JSN	Erosions: 2nd – 5th DIPs, all MCPs, the IPJ of the thumb, 7 bones in the wrist, all MTPs and the IPJ of the great toe JSN: 2nd – 5th DIPs, all MCPs, 6 joints in the wrist and all MTPs	Erosion 270 JSN 200	Erosion, JSN and widening, shaft periostitis, juxta-articular periostitis, periostitis in the wrist, and tuft resorption
van der Heijde modified Sharp	(van der Heijde 2000)	50 for erosions 52 for JSN	Erosions: all DIPs/IPs, MCPs, two 1st metacarpal bones, two radius and ulnar bones, two multangular units (trapezium and trapezoid combined), all MTPs and the IPJs of the great toes JSN: all DIPs/IPs, MCPs, two 3rd, 4th and 5th CMCJs, two multangular-navicular joints, two capitate-navicular-lunate joints, two radiocarpal joints, ten MTPs and the IPs of the great toes	Erosion 320 JSN 208	Erosion, JSN, ankylosis, pencil-in-cup, gross osteolysis

JSN: joint space narrowing

For axial disease, scoring systems are largely derived from AS, but both the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) and Bath Ankylosing Spondylitis Radiology Index (BASRI) have been validated in a cohort of patients with PsA (Lubrano et al. 2009b). A modification of these specific to axial PsA has also been described, termed the Psoriatic Arthritis Spondylitis Radiology Index (PASRI) (Lubrano et al. 2009a). This also scores the posterior elements of the spine.

Radiographs are quick to perform and useful for assessing chronic bony changes, with well validated scoring systems published.

2.3.2 Magnetic resonance imaging in psoriatic arthritis

Magnetic resonance imaging uses a strong magnetic field to alter the axis of protons within the body. Radiofrequency sources are then used to cause the nuclei to resonate and the radio wave signals that this generates are detected and used to create the images. The duration that it takes for the tissues to relax after the radiofrequency source is switched off is different for different tissues (based on their fat and water content) and allows differentiation between the tissues.

Magnetic resonance imaging has shown great promise for the imaging of PsA. Unlike conventional radiography, MRI is also able to demonstrate soft tissues including cartilage, synovium, tendons and ligaments. Unlike ultrasonography, MR is able to reveal bony changes such as osteitis and image the spine. It is therefore useful for imaging arthritis, enthesitis, dactylitis, and axial disease. Other advantages include the lack of radiation and the ability to standardise sequences and score imaging at distant sites for multi-centre studies. Some tissues and sequences require intravenous contrast administration, which is not possible in all patients. MRI remains expensive, time consuming and at times, uncomfortable for patients. Movement artefact may also degrade image quality. For peripheral arthritis and enthesitis, MRI remains a research tool, but for spinal imaging it has a place in clinical care. MR imaging of enthesitis in PsA will be covered in

detail in section 2.4.1.2 and MRI studies of the DIP joint and nail will be covered in section 2.5.5.1.

Typical features of peripheral joint arthritis are similar to those seen in rheumatoid arthritis. Synovitis, joint effusion, bone marrow oedema and erosions are common, as is soft tissue involvement and tenosynovitis (Tehranzadeh et al. 2008). Bone proliferation and periosteal enhancement may also be seen (Ghanem et al. 2007). Peripheral joint arthritis may appear as high signal on T2 weighted images and contrast enhancement on T1 weighted post contrast images. Unlike in rheumatoid arthritis where the main changes occur within the synovial joint, active joints in PsA may have quite extensive surrounding inflammation, affecting the joint capsule, surrounding tendons and ligaments and the soft tissue (Jevtic et al. 1995). MRI is more sensitive than radiographs for detecting both inflammation and damage in PsA (Wiell et al. 2007). Bone marrow oedema lesions are important as they predict the later development or erosions (Savnik et al. 2002). A cross-sectional study of erosive PsA including arthritis mutilans also found an association between bone oedema and current radiographic damage (Tan et al. 2009).

In a comparative study with RA, periostitis and synovitis of the PIP joints occurred more frequently in PsA. Erosions were more frequent in RA compared to PsA and there was no different in the frequency of bone marrow oedema or tenosynovitis (Schoellnast et al. 2006). A separate study found the only differences on imaging between RA and PsA were the DIP involvement in PsA along with bony proliferation (Wiell et al. 2007). In early arthritis (symptom duration < 1 year), the presence of enthesitis or diaphyseal bone oedema differentiated PsA from RA, both with a specificity of 100% and sensitivities of 71% and 65% respectively (Narvaez et al. 2012). In contrast, Marzo-Ortega et al. found that MRI of the MCP joints was not able to differentiate reliably between early RA and PsA (<24 months duration), although a small subgroup of PsA patients had extracapsular enhancement and bone marrow oedema (Marzo-Ortega et al. 2009).

In another study assessing the sensitivity and specificity of clinical examination of the MCP joint, an association was seen between clinical tenderness and MRI synovitis (Stone et al. 2009). Stress pain (pain at the extreme of passive extension) showed an association with bone oedema. No association was seen between clinical swelling and underlying MRI findings, suggesting that tenderness may be more discriminative than swelling. Clinical examination was not as sensitive as MRI in detecting synovial pathology.

An MRI study of dactylitic digits has shown widespread changes, with synovitis and soft tissue oedema the most common findings, but tenosynovitis and bone marrow oedema also noted (Healy et al. 2008a). The degree of bone marrow oedema varied from patient to patient. Soft tissue oedema was seen to be circumferential rather than localised to any particular structure.

Little data are available on the imaging of spinal disease in PsA. A study of 103 patients with PsA (not selected on the basis of axial symptoms) in whom 68 agreed to undergo an MR scan found clinical features of sacroiliitis in 35% and MRI features in 38% patients (Williamson et al. 2004b). The correlation between clinical and MRI features was low, with a positive predictive value of clinical assessment in predicting MRI sacroiliitis of 42%. The best clinical predictor of MRI sacroiliitis was restricted spinal movements on examination. HLA B27 was not significantly associated with MRI findings.

To meet the criterion of ‘truth’ in the OMERACT filter, it is important that what is believed to represent inflammation on MRI does indeed represent histological inflammation. For sacroilitis this was demonstrated in a biopsy study in patients with spondyloarthropathies including PsA (Bollow et al. 2000). T cells and macrophages were the most common inflammatory cells seen in actively inflamed sacroiliac joints and a correlation was seen between cellularity and the degree of MRI sacroiliitis. For synovitis, no data is available in PsA but two studies in RA have confirmed a correlation between MRI appearances and histological inflammation (Konig et al. 1990; Gaffney et al. 1995).

Until the development of a validated scoring system for PsA, a variety of methods have been used. A scoring system for the MR appearances of dactylitis was documented in one observational study (Healy et al. 2008a). At each joint level, eight features were recorded as present (score 1) or absent; synovitis, bone oedema, subcutaneous oedema, flexor tenosynovitis, extensor tenosynovitis, plantar / volar plate enhancement, collateral ligament enhancement and erosions. For the thumb and great toe, sesamoiditis was also scored. The maximum score was 17 for the thumb or great toe and 24 for all other digits. With change in treatment, reductions in the MRI score were seen, but on an individual digit level, correlations were not seen between clinical findings and the MRI score. In an adalimumab study, MRI scans were performed of the most active wrist or knee joint (Anandarajah et al. 2010). These were scored for bone marrow oedema (score 0-5), bone erosions (score 0-5), synovitis (score 0.3) and effusion (score 0.5). Bone marrow oedema and erosions were scored at 13 sites in the wrist and at three sites in the knee. Synovitis and effusion were scored at three sites in the wrist and one in the knee. Scans were scored by consensus and therefore no inter-observer reliability data is available. The RCT for abatacept used a modification of the Rheumatoid Arthritis Magnetic Resonance Imaging Scoring (RAMRIS) designed for RA. A trend to improvement in erosion, synovitis and effusion scores was seen (Mease et al. 2011).

Improvements in MRI-determined bone marrow oedema have been shown in patients with PsA receiving treatment with adalimumab (Anandarajah et al. 2010). Surprisingly though, the erosion score increased over 24 weeks of treatment and although synovitis improved in nine joints, it worsened in eight and was static in three. In an open label study with infliximab in PsA, in order to reduce concerns over placebo response in subjective patient-reported outcome measures, MRI was performed in eight patients. A reduction in Gadolinium uptake was seen in all patients at ten weeks (Antoni et al. 2002). For a study using etanercept, bone marrow oedema volume in a target joint was chosen as the MRI outcome measure (Anandarajah et al. 2008). The overall BMO volume decreased in nine

patients and increased in four after six months treatment but the majority of patients (even those with an overall improvement) had new or worsening areas of bone oedema on the six month scans. A study using infliximab found significant reductions in both synovitis and bone marrow oedema on MRI scans of the affected hand or knee after 20 weeks treatment, with 7/9 patients having complete resolution of bone marrow oedema (Marzo-Ortega et al. 2007a).

The development of a PsA-specific scoring method for MRI scans of the hands was first described in 2007 as a modification of the RAMRIS (McQueen et al. 2007). This was initially termed the Psoriatic Arthritis Magnetic Resonance Imaging Scoring system (PAMRIS) but was later renamed the PsAMRIS. The framework was taken from the RAMRIS but with the addition of features specific to PsA. In initial development, moderate to very good interreader reliability was seen for bone marrow oedema and erosions, but reliability was lower for synovitis (particularly in the DIP joints), extra-capsular inflammation and tendinopathy (McQueen et al. 2007). The scoring system was refined and definitions were proposed for key pathologies (Ostergaard et al. 2009). This was then tested in a cross-sectional and a longitudinal study (McQueen et al. 2009). While reliability was good for some features, peri-articular inflammation and DIP disease scores were less reliable. A multi-reader exercise was then performed in a group of patients commencing treatment and followed for 12 months (Boyesen et al. 2011). Generally, reliability was good, and sensitivity to change in synovitis, flexor tenosynovitis and periarticular inflammation was demonstrated. The PsAMRIS has since been used in a treatment study involving zolendronic acid (McQueen et al. 2011).

Dynamic contrast-enhanced MRI is a newer technique in development which assesses enhancement to study vascularity but is currently showing inconclusive results in its ability to differentiate synovitis between RA, OA and PsA (Cimmino et al. 2005; Schwenzer et al. 2010; Schraml et al. 2011; Cimmino et al. 2012). One study has been published on whole body MR, which gives a good overview of multiple joint areas including the spine in one scan (Weckbach et al. 2011). Enthesitis was the most common

finding, followed by synovitis and bone marrow oedema. The most common sites for enthesitis were around the spine and pelvis. MRI was more sensitive than clinical examination in detecting enthesitis and synovitis. In 73% patients the treatment was changed as a result of the findings on MR. Three patients who underwent a second scan after a change in treatment had improvements noted on imaging.

Magnetic resonance imaging has an important place in research into PsA, with its potential to study the multiple facets of the disease, but remains limited by cost, accessibility and discriminative ability from widespread use in clinical practice.

2.3.3 Ultrasound in psoriatic arthritis

Ultrasound uses high frequency sound waves to generate images. These sound waves are transmitted into the body by the probe, and some are reflected back when there is a boundary between different types of tissue (water, fat, bone). The time taken for these reflections or echoes to return back to the probe is used to calculate the distance involved and produce an image. Resolution is determined by the pulse length, probe frequency and frame rate. Higher frequency probes give greater lateral resolution but lower depth penetration.

Ultrasound has increasingly been used in rheumatology clinical practice and research over the part twenty years. Key advantages include the ease of use, lack of radiation, acceptability to patients, low cost, widespread availability, high sensitivity and the ability to study many joints in one assessment. Disadvantages include the fact that ultrasound is very operator dependent and also as it is a real-time imaging modality, this limits its use in multicentre studies as images cannot be scored centrally. Modern scanners with high frequency transducers now have very good resolution for detecting very small structures or abnormalities such as erosions. The majority of data on rheumatology ultrasound comes from the RA literature, showing that power Doppler (PD) ultrasound identifies

vascular abnormalities known to be associated with inflammation, and that these relate to both later damage and response to treatment (Naredo et al. 2008; Kurosaka et al. 2010; Hammer et al. 2011). There has been increasing interest in the use of ultrasound in PsA partly because of the ability to study not just synovitis but also enthesitis and dactylitis. Ultrasound also has a greater sensitivity to detect inflammation than clinical examination (Milosavljevic et al. 2005; Delle Sedie et al. 2010; Delle Sedie et al. 2011).

Typical features include synovitis, erosions, tenosynovitis, enthesitis and soft tissue oedema. In the peripheral joints ultrasound features include joint effusion, synovial proliferation, intra-articular PD signal (suggesting active inflammation) and bone erosion (Gutierrez et al. 2010). Tendon involvement may demonstrate tenosynovitis, areas of hypoechogenicity or tendon tears (Gutierrez et al. 2010). In dactylitic digits, synovitis, tenosynovitis and soft tissue oedema may all occur (Kane et al. 1999; Gutierrez et al. 2010). In an earlier dactylitis study, only flexor tenosynovitis was demonstrated on ultrasound, without soft tissue or joint involvement (Olivieri et al. 1996).

A comparative study of MCP disease in RA and PsA using ultrasound found peritenon extensor inflammation and extra-articular PD signal to be characteristic of PsA and to help differentiate these diseases (Gutierrez et al. 2011b). These findings were confirmed in another study where RA and PsA fingers were compared, again detecting synovitis, tenosynovitis and erosions but observing extra-articular abnormalities to be characteristic of PsA and not seen in RA (Fournié et al. 2006). The most common seen here were enthesophytes, enthesopathy, periosteal reaction and soft tissue thickening. Ultrasound may be useful in helping confirm a diagnosis of PsA in psoriasis patients with articular symptoms (De Simone et al. 2011). In a study of early PsA patients (<1 year symptoms), no radiographic abnormalities were seen, but ultrasound confirmed an effusion in the target joint in every patient (Bonifati et al. 2012). Ultrasound has been shown to have good specificity in PsA, with greater sensitivity in detecting erosions than x-rays (Wiell et al. 2007). Ultrasound was more sensitive than clinical

examination in detecting synovitis. In a study comparing different imaging modalities for assessing the peripheral joints in PsA patients, ultrasound had a lower sensitivity in detecting synovitis and joint effusion than MRI, but better sensitivity than MRI in detecting erosions (Weiner et al. 2008). This study was limited by not using PD ultrasound as part of the assessment. In one of the earlier studies, ultrasound showed good correlation with the clinical course in PsA patients undergoing synovectomy, showing promise as an objective measure for monitoring treatment (Fiocco et al. 1996).

There are currently no validated widely used scoring systems for the ultrasound assessment of joints or dactylitis in PsA, although OMERACT has set out definitions of pathological findings in order to help standardise descriptions (Wakefield et al. 2005). A composite scoring system called the Five Targets PD for Psoriatic Disease (5TPD) is in development and preliminary data has recently been published (Gutierrez et al. 2012). This measures PD signal at five targets (skin, nails, joints, tendons and enthesitis, with a semiquantitative score of 0-3 at each target, giving a maximum possible score of 15. In the preliminary study, all clinically involved areas were assessed, and the maximum score for each target was recorded. Reductions in the 5TPD were seen with treatment. Validated scoring systems are needed and this score may offer some promise. One of the difficulties with the heterogeneous nature of PsA is that composite scores may make it more difficult to study treatment efficacy on different aspects of the disease. In a treatment study using adalimumab, ultrasound assessment was used as an outcome assessment, with the most clinically involved joint being scanned, and abnormalities as per the OMERACT definitions being recorded and scored on a semiquantitative basis (Teoli et al. 2012). With this method, significant improvements in effusion, synovial proliferation and PD signal were seen. Several other studies have used similar semiquantitative measurements or measurements of synovial thickness (Fiocco et al. 2005; Milosavljevic et al. 2005; De Agustin et al. 2012).

Ultrasound is a widely used technique in studying PsA, currently used more in research than in clinical practice. The most significant ongoing limitation is the lack of well validated and widely accepted scoring systems.

2.4 Enthesitis

2.4.1 Enthesitis in psoriatic arthritis

As described earlier enthesitis, or inflammation at insertions such as ligament or tendon attachments to bone, is a characteristic feature of PsA. It may be assessed clinically but a number of imaging modalities have also been used.

2.4.1.1 Ultrasound imaging of enthesitis in psoriatic arthritis

One of the earliest descriptions of the ultrasound appearances of enthesopathy suggested that oedema at the tendon insertion was the most common feature, and that it was frequently missed on clinical examination (Lehtinen et al. 1994). Typical features are tendon thickening, calcifications, enthesophytes (generally the most common finding), erosions, bony irregularities, PD signal at the enthesis, PD signal in the tendon, bursitis, tendon hypoechogenicity or loss of the normal fibrillar tendon structure (Balint et al. 2002; Gutierrez et al. 2010; Iagnocco et al. 2012).

In 2005 the OMERACT group published a consensus definition for the ultrasound definition of enthesopathy: ‘Abnormally hypoechoic (loss of normal fibrillar architecture) and/or thickened tendon or ligament at its bony attachment (may occasionally contain hyperechoic foci consistent with calcification), seen in 2 perpendicular planes that may exhibit Doppler signal and/or bony changes including enthesophytes, erosions, or irregularity’ (Wakefield et al. 2005).

Enthesitis can occur in multiple areas around the body. The most common sites are in the lower limb, but it can also occur in the upper limb and enthesitis of the deltoid proximal insertion has been demonstrated in 17% PsA patients with current shoulder pain (Falsetti et al. 2002).

With increasing interest in the different areas of the enthesis organ, it has been shown that ultrasound has the capability to visualise the entheseal fibrocartilage (a structure of around 0.5mm thickness), with evidence of loss of the fibrocartilage at sites of entheseal erosion (Aydin et al. 2010a). Surprisingly one study has shown that erosions as seen on ultrasound may not be a permanent structural alteration, as 25% had disappeared after six months follow-up, and 50% had resolved after 12 months (de Miguel et al. 2011a). The authors suggested that this may be due to new bone formation as part of the SpA pathological processes.

Little data are available on the prevalence and characteristics of enthesitis amongst the subtypes of PsA. SAPHO (synovitis, acne, pustulosis, hyperostosis) syndrome has been described as a subtype of SpA. In a small study, US evidence of enthesopathy (largely subclinical) was significantly more common in SAPHO patients than controls, and was only seen in the subgroup of patients with palmoplantar pustulosis or palmoplantar pustular psoriasis as the skin lesion, not in patients with only acne or hidradenitis suppurativa, suggesting that these subgroups may be phenotypically important (Queiro et al. 2012a).

One of the key problems of ultrasound assessment of enthesitis is where to draw a line between ‘normal’ and ‘disease’ in view of the high prevalence of abnormalities in healthy controls. Particularly in the lower limbs these findings may be mechanical. Herein lies the importance of recruiting appropriate controls to studies in order not to over-call minor changes which are in fact within the normal range.

The majority of studies have found that clinical examination underestimates the prevalence of enthesitis in PsA, suggesting that subclinical enthesitis is common. The study by Balint et al. assessing enthesopathy in the lower

limbs in SpA patients found clinical enthesitis in 22% of the sites examined, and US abnormalities in 56% sites. In comparison to ultrasound, they found clinical examination to have a sensitivity of 23% and a specificity of 80% in detecting enthesitis (Balint et al. 2002). Data on quadriceps tendon enthesitis also found an underestimation by clinical examination, with 45% PsA patients having ultrasound evidence of enthesitis, but of these, only 45% had clinical enthesitis (Frediani et al. 2001). When assessing all the entheses at the knee, ultrasound was shown to be more sensitive overall than clinical assessment in detecting joint inflammation and enthesitis. However, in 14 patients, clinical examination suggested enthesitis while ultrasound was normal (Delle Sedie et al. 2010). One key difference in this study is that enthesophytes were not included in the scoring system as they were felt to be common and non-specific. A study in patients with longstanding PsA found subclinical enthesitis in 13% of the sites assessed (Marchesoni et al. 2012). In SpA patients, 30% entheses assessed had subclinical enthesitis seen on ultrasound (D'Agostino et al. 2003). A study validating the Leeds Enthesitis Index found a very poor correlation between clinical and ultrasound findings (Ibrahim et al. 2010). In AS, abnormalities were found frequently in both the upper and lower limbs (Spadaro et al. 2011). The study found a high prevalence of both subclinical enthesitis but also sites which were clinically tender but with a normal ultrasound.

In contrast, in a study of patients with early PsA, only 4% non-tender entheses had a positive ultrasound (definited as a grey scale score >1 or a PD score >0), suggesting a very low level of subclinical enthesitis (Freeston et al. 2012). Those areas of subclinical enthesitis also tended to be in the lower limb and the authors suggested a potential role of mechanical stress here. A grey scale score of 1 was considered as normal as this can occur in normal subjects, and this may potentially explain the discrepancy between this and other studies. The study also found that 13% entheses had a positive finding on clinical examination but a normal ultrasound, suggesting that clinical examination was overestimating the degree of enthesitis. In a quarter of these, the tender enthesis was adjacent to a tender joint, suggesting that this may have influenced the

clinical finding. In the control group (n=10), only 1% entheses had a positive low grade PD signal but grey scale findings were common, with 50% patients having a bony spur at the calcaneum and 10% having intratendinous calcification in the inferior patellar tendon.

Although US features of enthesopathy were more severe in PsA than RA patients overall, on a patient level it was not possible to differentiate the two diseases using an ultrasound of the entheses (Iagnocco et al. 2012). At the quadriceps tendon insertion, differences were noted between PsA and RA patients, with more PsA than RA patients having ultrasound evidence of enthesitis (45% vs 7.5%) but RA patients being more likely to have a joint effusion (95% vs 60%). Isolated enthesitis (without joint effusion) was only seen in PsA patients. RA patients were more likely to have inflammatory features (oedema, tendon thickening and hypoechogenicity) while features of new bone formation were almost exclusively seen in PsA (Frediani et al. 2001). In the finger, entheseal abnormalities were seen in a subset of PsA patients (enthesophytes in 3/25 and distal phalanx enthesopathy in 4/25) while no enthesopathy was seen in RA patients (0/25) thus this did allow differentiation between the diseases, albeit with a low sensitivity (Fournié et al. 2006). At the MCP joint, the presence of peritenon extensor tendon inflammation potentially differentiated PsA and RA patients, occurring in 65.8% vs 0% (Gutierrez et al. 2011b). Interestingly when assessing the entheses at the heel, the frequency of enthesophytes was similar in OA and PsA (Falsetti et al. 2003). Inflammatory features were more common in PsA and RA than OA. Achilles enthesitis was seen in 8% PsA patients but not in OA or control subjects. Plantar fasciitis was not significantly more common in PsA than RA. The value of PD ultrasound in the diagnosis of SpA at an early stage was evaluated in a French cohort (D'Agostino et al. 2011). A finding of at least one vascularised enthesis using PD ultrasound gave a sensitivity of 76.5% and a specificity of 81.3% for the diagnosis of SpA. The Achilles tendon and lateral epicondyle were more frequently involved in SpA than non-SpA patients. A similar study in Spain found a significantly higher mean ultrasound enthesitis score in early SpA patients compared to

undifferentiated early SpA and controls (de Miguel et al. 2011b). No difference was seen in the overall US score or the pattern of abnormalities between patients with axial or peripheral disease. An US score of >20 had a sensitivity of 53.1%, a specificity of 83.3% and a positive likelihood radio of 3.26 for a diagnosis of SpA. The differential diagnosis of PsA and fibromyalgia can be difficult clinically, as enthesitis is manifest as tender points, and fibromyalgia is characterised by tender points. These can be situated quite close together, for example at the elbow. A study performed to address whether ultrasound may help in making this distinction was performed in Italy (Marchesoni et al. 2012). Interestingly, although all features of enthesopathy were significantly more common in PsA, the fibromyalgia patients also had frequent abnormalities on US (enthesopathy in 80% patients, inflammatory lesions 23% and entheseal PD signal 23%). The quadriceps tendon and Achilles tendon were the most frequently abnormal. Erosions were only seen in PsA patients. Fibromyalgia patients were more likely to have clinically tender but ultrasonographically normal sites than PsA patients (37% vs 8%). A finding of US-detected abnormalities in at least three entheses predicted a diagnosis of PsA with a sensitivity of 72% and a specificity of 76%.

Several different ultrasound scoring systems have been described for enthesitis which include features such as thickening, hypoechoic change, bone erosion and new bone formation (see Table 5). The Madrid Sonographic Entheseal Index (MASEI) was proposed in 2009 after development in a cohort of SpA patients (de Miguel et al. 2009). The maximum total score is 136. An enthesis in the upper limb was included, in order to reduce the influence of mechanical factors. In comparing healthy controls and SpA patients, a score of ≥18 had a sensitivity of 83.3%, a specificity of 82.8% and a positive likelihood ratio of 4.87 in predicting a diagnosis of SpA. The GUESS score was proposed by Balint, with substantial to excellent intraobserver agreement demonstrated in the initial study (Balint et al. 2002). The disadvantages of the GUESS score are that it studies the lower limbs only, and does not include a PD assessment.

The ultrasound score proposed by Naredo showed excellent intraobserver reliability and responsiveness to change with treatment (Naredo et al. 2010). Morphological abnormalities, PD signal and bursitis scores all reduced with treatment, suggesting that these are indeed inflammatory features, while calcific deposits and cortical abnormalities were confirmed as more in keeping with structural damage. An ultrasound assessment of the same entheses as in the MASES clinical enthesitis index unusually found that clinical examination revealed more positive findings than ultrasound (Kiris et al. 2006). This scoring system includes more entheses around the axial skeleton than the others. Highly vascularised entheses were more likely to be tender. A scoring system for the Achilles tendon was proposed in order to demonstrate the validity of ultrasound in assessing entheses (Filippucci et al. 2009). Moderate to excellent interobserver and intraobserver agreement was seen for the overall score and all individual features except calcaneal bone irregularities, which were therefore then not included in the total score. The Sonographic Enthesitis Index (SEI) was developed in AS patients (Alcalde et al. 2007). All the healthy controls had an SEI score of 0. Of the AS patients, 41/44 had abnormalities seen on entheseal ultrasound. Good interobserver reliability was seen. A modification was subsequently proposed to the SEI to add a PD assessment (Hamdi et al. 2011). With this, the Doppler score correlated well with disease activity measures and the total score correlated well with clinical enthesitis indices. The GUESS score has been the most widely used.

One of the key problems of ultrasound assessment is the fact it is operator dependent. A process to improve reliability was recently reported by D'Agostino (D'Agostino M et al. 2009). The first step was to assess the interobserver and intraobserver reliability of five sonographers. Consensus definitions and guidelines were then produced within the group regarding scanning technique, a scoring system and definitions of abnormalities. Reliability was then reassessed. After a further year, reliability was again re-assessed. Marked improvements were seen in the reliability of ultrasound assessments and scoring for Doppler findings.

Table 5. Scoring systems for ultrasound evidence of enthesitis in SpA patients

Name (Reference)	**Designed in PsA, AS or SpA**	**Entheses included**	**Power Doppler included?**	**Features scored**
GUESS (Balint et al. 2002)	SpA	• Quadriceps tendon into superior border of patella • Superior patellar tendon insertion • Inferior patellar tendon insertion • Achilles tendon • Plantar fascia	No	Four aspects scored at each enthesis: tendon thickness (> stated normal thickness for each site), erosions, enthesophyes and bursitis (where applicable – not scored at plantar fascia or superior patellar tendon insertion) When present, scored as one point for each abnormality at each site, giving maximum score of 36 Soft tissue score (entheseal thickness and bursitis) and bone score (erosions and enthesophytes) may also be calculated separately
- (Falsetti et al. 2003)	PsA	• Achilles tendon • Plantar fascia	No	Abnormalities graded as 0-3 Enthesophytes, enthesitis (hypoechogenicity and thickening), bursitis, erosions, panniculitis

Name (Reference)	**Designed in PsA, AS or SpA**	**Entheses included**	**Power Doppler included?**	**Features scored**	**Name (Reference)**
- (D'Agostino et al. 2003)	SpA	• Common extensor origin at the elbow • Common flexor origin at the elbow • Gluteus insertion at the greater trochanter • Pubis enthesis • Quadriceps tendon into patella • Superior patellar tendon insertion • Achilles tendon • Plantar fascia • Tibialis anterior insertion	Yes	Stage 0 Stage 1 Stage 2a Stage 3a Stage 2b Stage 3b	Normal Vascularisation at the cortical junction without abnormal findings in B mode Vascularisation associated with swelling and/or decreased echogenicity at the cortical junction in B mode Same as stage 2a, plus erosions of cortical bone and/or calcifications of enthesis, and optional surrounding bursitis Abnormal findings in B mode as in stage 2a, but without vascularisation Abnormal findings in B mode as in stage 3a, but without vascularisation

Name **(Reference)**	**Designed in PsA, AS or SpA**	**Entheses included**	**Power Doppler included?**	**Features scored**
MASES (Kiris et al. 2006)	AS	• 5th lumbar spinous process • 1st and 7th costochondral joints • Posterior superior iliac spine • Anterior superior iliac spine • Iliac crest • Achilles tendon	Yes	• Focal changes (hypoechogenicity within the tendon) • Calcification of the tendon • Cortical reactive changes (reabsorption, new bone formation, irregularity) • Bursitis The above scored as present or absent (0-1) Vascularisation (scored 0-3)

Name (Reference)	Designed in PsA, AS or SpA	Entheses included	Power Doppler included?	Features scored
SEI (Alcalde et al. 2007)	AS	• Quadriceps tendon into superior border of patella • Superior patellar tendon insertion • Inferior patellar tendon insertion • Achilles tendon • Plantar fascia	No	Separate scores for inflammation and chronic change Inflammation: entheseal thickening, hypoechogenicity, peritendinous oedema, bursitis (where applicable) Chronic change: tears, loss of thickness, intratendinous calcification, bone erosion Each feature scored as present (1) or absent (0) Maximum inflammation score 36, chronic score 40, total score 76
- (McGonagle et al. 2008)	SpA	Achilles tendon (3 sites: proximal and distal halves of the enthesis, calcaneal superior tuberosity)	No	Erosions Bone spurs (semiquantitative scoring for size 0-3) Hypoechoic thickening or loss of fibrillar architecture

Name (Reference)	**Designed in PsA, AS or SpA**	**Entheses included**	**Power Doppler included?**	**Features scored**
- (Iagnocco et al. 2009)	SpA	Achilles tendon	Yes	Lesions scored: tendon hypoechogenicity, tendon thickening, intra-tendinous calcifications, enthesophytes, bony erosions, bony cortex irregularities, presence of Doppler signal at the level of the bony attachment, presence of intratendinous Doppler signal, bursal enlargement, tendon tears (partial or full thickness) Each item scored dichotomously as present / absent (1/0) then also on semiquantitative scale (0-3)

Name (Reference)	Designed in PsA, AS or SpA	Entheses included	Power Doppler included?	Features scored
MASEI (de Miguel et al. 2009)	SpA	• Distal brachial triceps tendon • Quadriceps tendon into superior border of patella • Superior patellar tendon insertion • Inferior patellar tendon insertion • Achilles tendon • Plantar fascia	Yes	Lesions scored at each site: calcifications, bursae, erosions, power Doppler signal in the bursa or tendon at the enthesis, thickness and structure Score for calcification: irregularity of the cortical bone, enthesophytes and ossifications Thickness measured at the point of maximal thickness at the insertion (> stated normal thickness for each site) Abnormal structure defined as loss of fibrillar pattern, hypoechonicity or fusiform swelling at the enthesis Each item scored as 0 (absent) or 1 (present) except calcifications (scored 0-3), erosion (0 or 3 if present) and Doppler signal (0 or 3)

Name (Reference)	**Designed in PsA, AS or SpA**	**Entheses included**	**Power Doppler included?**	**Features scored**
- (D'Agostino M et al. 2009)	SpA	• Common extensor origin at the elbow • Quadriceps tendon into superior border of patella • Superior patellar tendon insertion • Achilles tendon • Plantar fascia	Yes	Morphologic abnormalities: increased thickness or hypoechogenicity of enthesis insertion (score 1) Structural abnormalities: calcifications and /or enthesophytes (score 1), erosions (score 1) Vascularisation at the enthesis insertion into the cortical bone (score 0-3)

Name (Reference)	**Designed in PsA, AS or SpA**	**Entheses included**	**Power Doppler included?**	**Features scored**
- (Filippucci et al. 2009)	SpA	Achilles tendon only	Yes	Based on OMERACT definition of enthesopathy Separate scores for inflammation and tissue damage Inflammation score: tendon hypoechogenicity, tendon thickening, entheseal hypoechogenicity, bursal effusion, PD signal at the tendon level, PD signal at entheseal level, PD signal at bursal level Scores calculated as either presence / absence (maximum total 7) or semiquantitative (score 0-2) (maximum total 14) Tissue damage score: intratendinous calcification, entheseal calcification, enthesophytes and bone erosions Scores calculated as either presence / absence (maximum total 4) or semiquantitative (score 0-2) (maximum total 8)

Name (Reference)	Designed in PsA, AS or SpA	Entheses included	Power Doppler included?	Features scored
- (Naredo et al. 2010)	SpA	• Common extensor origin at the elbow • Common flexor origin at the elbow • Quadriceps tendon into superior border of patella • Superior patellar tendon insertion • Inferior patellar tendon insertion • Achilles tendon • Plantar fascia	Yes	Lesions scored as present or absent: morphologic abnormalities (hypoechogenicity, thickening), entheseal calcific deposits, entheseal cortical abnormalities (erosion, enthesophytes), adjacent bursitis, intraenthesis PD signal at the insertion, perienthesis PD signal at tendon body or bursa

Name **(Reference)**	**Designed in PsA, AS or SpA**	**Entheses included**	**Power Doppler included?**	**Features scored**
- (Ibrahim et al. 2010)	PsA	• Common extensor origin at the elbow • Medial femoral condyle • Achilles tendon	Yes	Lesions scored as present (1) or absent (0): Inflammation features: entheseal vascularisation (with PD), bursitis, entheseal thickening and perientheseal soft tissue oedema Damage score: erosions, enthesophytes,
Modification of the SEI (Hamdi et al. 2011)	AS	• Quadriceps tendon into superior border of patella • Superior patellar tendon insertion • Inferior patellar tendon insertion • Achilles tendon • Plantar fascia	Yes	As for the SEI with the addition of PD findings (scored 0 or 1) Total score range 0-76

Name **(Reference)**	**Designed in PsA, AS or SpA**	**Entheses included**	**Power Doppler included?**	**Features scored**
- (Freeston et al. 2012)	PsA	• Common extensor origin at the elbow • Inferior patellar tendon insertion • Achilles tendon • Plantar fascia	Yes	Based on OMERACT US group recommendations Findings divided into 'active inflammation' and 'structural change'. GS and PD each scored semiquantitatively (range 0–3) GS score designated as a composite score of tendon/aponeurosis thickening and hypoechogenicity (loss of fibrillar pattern). Highest score for either parameter used as the final GS score GS score of ≤1 considered as normal Adjacent bursal effusion scored 0–3 where present Erosion, bony spur, and intratendinous calcification (all features of structural change), recorded as present or absent Erosions only scored if identified in two planes and located within the area into which the tendon or aponeurosis typically inserts

Name (Reference)	Designed in PsA, AS or SpA	Entheses included	Power Doppler included?	Features scored
- (Iagnocco et al. 2012)	PsA	• Common extensor origin at the elbow • Gluteus insertion at the greater trochanter • Quadriceps tendon into superior border of patella • Superior patellar tendon insertion • Inferior patellar tendon insertion • Achilles tendon • Plantar fascia	Yes	Based on the OMERACT definition of enthesopathy Features included: hypoechogenicity, thickening, calcifications, enthesophytes, erosions, bony irregularities, PD signal at the enthesis, PD signal in the tendon, bursitis and tendon lesions Items scored on a semiquantitative (0-3) or dichotomous basis (0-1) Scores calculated as a total for each entheseal site and globally

Name (Reference)	Designed in PsA, AS or SpA	Entheses included	Power Doppler included?	Features scored
- (Marchesoni et al. 2012)	PsA	• Common extensor origin at the elbow • Gluteus insertion at the greater trochanter • Quadriceps tendon into superior border of patella • Superior patellar tendon insertion • Inferior patellar tendon insertion • Achilles tendon • Plantar fascia	Yes	Based on OMERACT definition of enthesopathy Scored for tendon hypoechogenicity, tendon thickening, intratendinous calcification, enthesophytes, erosions, bone cortex irregularities and PD signal at the bony insertion Semiquantitative scoring (0-3) except cortex abnormalities (present or absent) Active inflammation: hypoechogenicity, PD signal at the enthesis Previous inflammation: erosions

A number of studies have used ultrasound scans of the entheses to monitor treatment response in SpA patients. With sulphasalazine treatment in SpA patients, no improvement was seen in ultrasound parameters of enthesopathy over six months treatment (Lehtinen et al. 1995). A larger study of RA and AS patients commencing treatment with sulphasalazine monitored treatment response using the GUESS score and also found no improvement in US scores with treatment (Genc et al. 2007). Two SpA patients with refractory heel pain treated with infliximab had marked improvements both clinically and noted with ultrasound over 14 weeks (D'Agostino et al. 2002). A significant reduction in the morphology score, intraenthesis PD score, perienthesis PD score and bursitis score for a number of enthesis sites was seen in SpA patients after six months of treatment with TNF inhibitors (Naredo et al. 2010). The calcific abnormality score and cortical abnormality score (both more related to chronic damage) both increased during the study. Another study assessed only the Achilles enthesis, using the scoring system previously described by Filippucci (Filippucci et al. 2009), but recording the inflammatory features only as the damage features were not expected to change with treatment (Aydin et al. 2010b). These scores were summated to give a score for PD findings, a grey scale score and a total score. Scans were performed on 43 AS patients prior to and after two months of TNF inhibitor therapy. Significant reductions were seen in the grey scale and total scores, the PD score reduced but the difference was not statistically significant. The score least affected by the treatment was the tendon thickness.

2.4.1.2 Magnetic resonance imaging of enthesitis in psoriatic arthritis

The majority of studies on the imaging of enthesitis have used ultrasonography but descriptions of the MR appearances of enthesitis are available. One key advantage of MRI over ultrasound in the assessment of enthesitis is the ability to detect bone marrow oedema at the insertion.

Enthesitis is not included in the PsAMRIS scoring system and no other validated scoring systems are available for enthesitis.

One of the earliest descriptions of the key role of enthesitis was by McGonagle and colleagues (McGonagle et al. 1998b). Ten SpA (including three PsA patients) and ten RA patients underwent MRI scanning of a swollen knee of recent onset. Three SpA patients and one RA patient had clinical evidence of enthesitis. All ten SpA patients had evidence of focal peri-entheseal high signal outside of the joint, while four of the ten RA patients also showed this. Focal bone marrow oedema at the enthesis was seen in six SpA patients and no RA patients. These findings led to the hypothesis that enthesitis is the common pathogenic mechanism shared in the spondyloarthropathies, and that it may occur as a primary pathology rather then secondary to synovitis.

Emad and colleagues described features of PsA on MRI scans of the knee joint (Emad et al. 2010). They found enthesitis to be a common finding at a number of sites around the knee, with bone oedema at the entheseal insertions. In a second study comparing patients with undifferentiated arthritis, RA and SpA including PsA, enthesitis was seen in 100% SpA patients, none of the RA patients and only 3/25 undifferentiated arthritis patients (Emad et al. 2009). The commonest sites were at the medial collateral ligament and the patellar tendon. In the hands, Jevtic used MRI and demonstrated characteristic features of enthesitis in PsA patients, with extra-capsular inflammation and thickening of the collateral ligaments (Jevtic et al. 1995). At the MCP joint, MRI was able to detect a characteristic pattern of extracapsular soft tissue enhancement suggestive of entheseal disease, but this was only seen in a small subgroup of patients (Marzo-Ortega et al. 2009). When compared to ultrasound at the finger, MRI was less sensitive at detecting insertional changes of the flexor and extensor tendons and capsular / extracapsular changes (Wiell et al. 2007).

In a cohort of SpA patients, MRI was performed of the heel (Feydy et al. 2012). Abnormalities were surprisingly common in both controls and SpA patients without heel pain (67% and 53% respectively) but were more

common in patients with current heel pain (81%). In control subjects (with mechanical back pain), enthesophytes of the plantar fascia were seen in 31%, enthesophytes of the Achilles in 17% and thickening of the Achilles in 21%. The only feature specific (94%) to SpA patients was oedema of the calcaneum but sensitivity was only 22%. Another study using ultrashort echo time imaging of the Achilles tendon found that quantitative measurements could be made, which were significantly different in SpA patients compared to healthy controls (Hodgson et al. 2012).

Whole body MRI was able to demonstrate widespread enthesitis in PsA patients, seen in 67% patients in the hips, 60% around the lumbar spine (particularly the interspinal ligaments) and 33% in the feet (Weckbach et al. 2011). MRI was more sensitive in detecting enthesitis than clinical examination, although in three patients clinical examination suggested enthesitis but MR was normal.

2.4.2 Subclinical enthesitis in psoriasis

Subclinical musculoskeletal inflammation, especially osteitis and periostitis, has been recognised since the 1970s in patients with psoriasis but no arthritis. Following the publication of the enthesitis theory of disease and the discovery that enthesitis is linked to osteitis, various groups have begun to look at the prevalence of enthesitis in patients with psoriasis but no arthritis. It is now been fairly well established that subclinical entheseal involvement is common in patients with psoriasis but without arthritis (see Table 6). The long term significance and predictive value of this is not yet known, especially as the prevalence of enthesitis in some reports is greater than the prevalence of PsA amongst psoriasis patients. The only available data on the predictive value of subclinical enthesitis in psoriasis patients comes from an Italian cohort, where the mean baseline GUESS score was significantly higher in patients who went on to develop PsA or OA than in those who remained asymptomatic after 3.5 years (Tinazzi et al. 2011). Looking at those developing PsA alone (without including OA) there was no

significant difference, but this was a small cohort (n=28). There are also little data available comparing the characteristics of enthesitis in psoriasis and PsA patients. Subclinical enthesitis has also been demonstrated in inflammatory bowel disease (Bandinelli et al. 2011), anterior uveitis (Munoz-Fernandez et al. 2009), scleroderma (Schanz et al. 2013), Behçet's (Ozkan et al. 2012) and renal dialysis patients (Gutierrez et al. 2011c).

Recently, positron emission tomography-computed tomography (PET-CT) has been used in psoriasis and PsA patients. In six patients with psoriasis (including one with PsA), three had no subclinical musculoskeletal involvement, the PsA patient had inflammation in joints, entheses, and muscles and two asymptomatic psoriasis patients had enthesitis and synovitis (Mehta et al. 2011). Increased uptake in the aorta and liver were also noted compared to controls. A second study found subclinical arthritis in 3/5 psoriasis patients but no PET-CT uptake in the joints of twenty control subjects (Takata et al. 2011). Intriguingly, a reduction in uptake was then seen after treatment with a TNF inhibitor.

Looking at the control cohorts, variable proportions are noted to have enthesitis also, depending on the imaging modality and scoring system used. With the GUESS score, 5% (2/40) of the controls for the inflammatory bowel disease study had an enthesophyte at the Achilles (Bandinelli et al. 2011). Also using the GUESS score, Gisondi found a correlation of the GUESS score with age, body mass index and waist circumference in the control cohort as well as the psoriasis patients (Gisondi et al. 2008). In the controls they saw no bursitis or erosions but enthesophytes were common (seen in 40% controls at the superior pole of the patella). Gutierrez also used the GUESS score and found evidence of enthesopathy in 8.4% of the sites assessed, predominantly entheseal thickness and enthesophytes, and commonest in the quadriceps enthesis and the Achilles (Gutierrez et al. 2011a). The 33 controls for the dialysis study were also assessed using the GUESS score, again entheseal thickness and enthesophytes were the most common finding, with a

positive finding in 16% enthesis sites and in 82% controls assessed (Gutierrez et al. 2011c). No PD signal was seen in the controls. Using the MASEI ultrasound score, 20 patients with non inflammatory eye diseases and 21 healthy controls were scanned (Munoz-Fernandez et al. 2009). 10% of the eye controls and 19% of the healthy controls had a score equal to or greater than the previously set positive MASEI cut-off score of 18. The most common lesion in either of the control groups was calcification or bone proliferation, seen most frequently at the Achilles. A high prevalence of subclinical synovitis and enthesopathy was seen in the study by Naredo (Naredo et al. 2011). US abnormalities were seen in 56.5% of the 46 controls, with both synovitis and enthesopathy seen in 15.2%. The Achilles tendon was the most common site of enthesopathy. In keeping with other studies, no controls had PD signal detected. These high rates are even after excluding the MTP joints from study because of the known high rate of synovitis in healthy controls

With MRI of the knee, no evidence of enthesitis or bone marrow oedema was seen in 20 controls (Emad et al. 2010). Likewise, with an MR of the foot, no abnormalities were seen in the control group (Erdem et al. 2008).

Two studies looked for factors predicting subclinical disease and found either no correlation between either demographic factors or the severity of skin psoriasis and subclinical disease, or only a correlation between increasing age and subclinical enthesopathy (Naredo et al. 2011; Emad et al. 2012).

Table 6. Studies assessing subclinical enthesitis and arthritis in psoriasis patients

Reference	Modality	No. of psoriasis patients	Control group	Findings in psoriasis patients	Findings in controls
(De Filippis et al. 2005)	US	24	None	33% patients had evidence of enthesopathy: extensor tendon effusions in the hand, flexor tendon nodulosis	N/A
(Emad et al. 2010)	MRI	6	20 healthy controls	5/6 showed enthesitis at the patellar tendon insertion, 1/6 at the medial patellofemoral ligament and 1/6 had bone marrow oedema	No entheseal changes, bone erosions or bone marrow oedema
(Emad et al. 2012)	MRI	48	20	MR evidence of enthesitis seen in 94% patients, soft tissue oedema in 54% knees scanned, bone marrow oedema in 21%, bone marrow oedema at the enthesis in 3% and erosions in 28%	Bone marrow oedema seen in 10%, cartilage lesions in 5%, no enthesitis seen

Reference	Modality	No. of psoriasis patients	Control group	Findings in psoriasis patients	Findings in controls
(Erdem et al. 2008)	MRI	26	10 healthy controls	92% patients with psoriasis had abnormal MRI of the foot (arthritis, enthesopathy, bone marrow oedema)	No abnormalities seen in control group
(Farouk et al. 2010)	US (Achilles only)	30	None	33% had US evidence of enthesopathy	N/A
(Gisondi et al. 2008)	US and x-ray	30	30 controls: other dermatology diagnoses	Mean GUESS score 7.9 - significantly higher than in controls ($p<0.0001$). Thickness of lower limb entheses and number of enthesophytes also higher.	Mean GUESS score 2.9
(Gutierrez et al. 2011a)	US	45	45 healthy controls	Mean GUESS score significantly higher than in controls ($p<0.0001$). Increased entheseal thickness in 16% entheses, enthesophytes in 15%, PD signal seen in 0.9%.	US enthesopathy in 8.4% entheses, no erosions or PD signal seen

Reference	Modality	No. of psoriasis patients	Control group	Findings in psoriasis patients	Findings in controls
(Namey et al. 1976)	Bone scintigraphy ^{99m}TcDP	12	12 controls: other hospitalised dermatology patients	Generalised periarticular uptake seen in all psoriasis patients. 86% of 168 joints scanned were abnormal	12% of 168 joints scanned were abnormal
(Naredo et al. 2011)	US	162	60 (outpatients with other skin diseases)	77% psoriasis patients had ultrasound abnormalities. Synovitis and enthesitis significantly more common than in controls. Entheseal or peri-entheseal PD signal seen in 11%. Subclinical synovitis most common in the knee, enthesitis at the Achilles	57% controls had ultrasound abnormalities, no PD signal seen
(Offidani et al. 1998)	MRI and x-ray	25	12 healthy controls	MRI abnormal in 68% psoriasis patients and x-ray in 32%. Subchondral changes in 36% patients on MRI	Only one joint cyst seen

Reference	Modality	No. of psoriasis patients	Control group	Findings in psoriasis patients	Findings in controls
(Raza et al. 2008)	Bone scintigraphy	50	25 controls: referred for bone scan for unrelated problem	35 of 50 patients (70%) with no clinical evidence for arthritis had a positive bone scan	16% controls had a positive bone scan

GUESS: Glasgow Ultrasound Enthesitis Scoring System. US: ultrasound. N/A: not applicable

2.5 Nail disease in psoriatic arthritis and psoriasis

2.5.1 Epidemiology

Nail disease is more common in PsA than in psoriasis (Gladman et al. 1987b; Jiaravuthisan et al. 2007; Love et al. 2007). It is recognised that the presence of nail disease in patients with psoriasis but without arthritis is predictive of future PsA development (Wilson et al. 2009a). The presence of nail disease has also been noted to be higher in patients with more severe psoriasis, those with a psoriasis history of more than five years duration and patients aged more than 50 (Tham et al. 1988). In that study a correlation was also seen between the presence of nail disease, scalp and periungual psoriasis, and the presence of arthritis. It is not yet clear whether the pathological changes causing nail disease are the same in both psoriasis and psoriatic arthritis. An association between nail disease and DIP joint disease has long been reported (Green 1968; Jones et al. 1994; Cohen et al. 1999; Kane et al. 2003; Scarpa et al. 2004; Williamson et al. 2004a). A small study in Japan found an association between nail fold psoriasis, DIP involvement and nail disease, but did not find an association between nail disease and the severity of the skin disease (Maejima et al. 2010). In 305 patients with nail psoriasis, nail disease was most commonly seen in the dominant thumb nail, raising the possibility that trauma may be involved in the pathogenesis (Rich et al. 2008). Another study found the highest prevalence in the fourth finger and the great toes (Brazzelli et al. 2012).

2.5.2 Pathology

The nails have an important function in protecting the tip of the finger and improving dexterity. The nail plate sits on the nail bed and is formed by the nail matrix (Figure 2 and 3). The nail bed has tiny longitudinal ridges, running from the lunula to the tip of the nail, these help attach the nail plate

to the nail bed and also contain blood vessels which are responsible for splinter haemorrhages (Zaias 1990).

Figure 2. Diagrammatic representation of the finger tip and nail

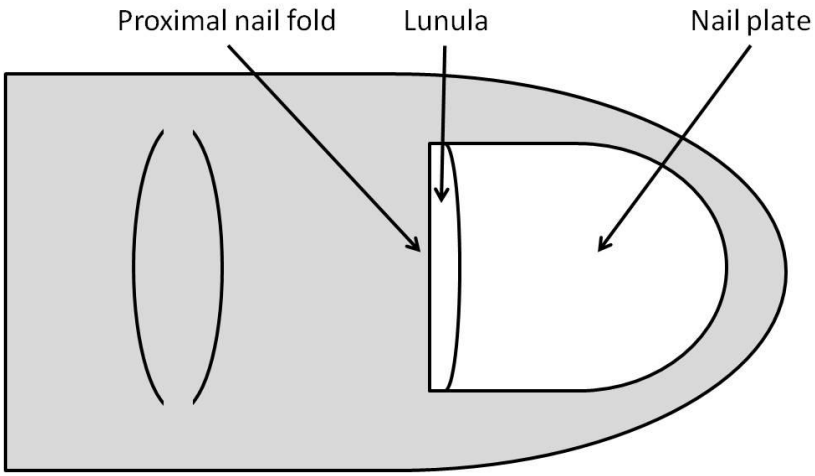
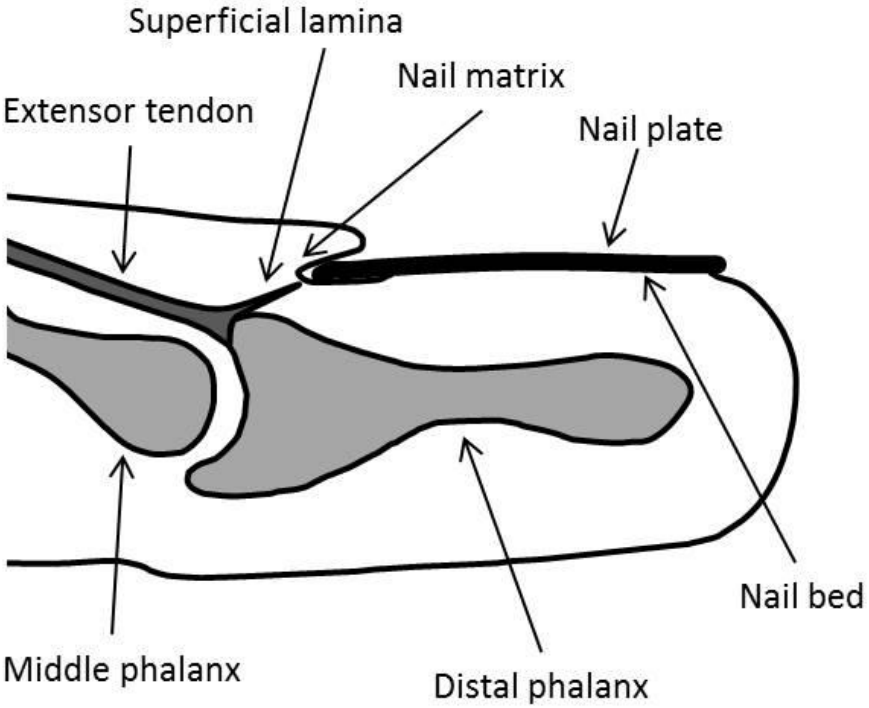


Figure 3. Diagrammatic representation of a cross section of the distal phalanx



Various types of psoriatic nail disease are recognised, and more than one type frequently co-exists in the same patient and even in the same nail. Nail changes may be divided into those abnormalities generally thought to

be associated with the nail plate and those with the nail matrix (Table 7 and Figure 4 and 5).

Table 7. Nail changes seen in psoriasis

Nail Plate	**Nail Matrix**
Oil drop discolouration	Leuconychia
Splinter haemorrhages	Red spots in the lunula
Subungual hyperkeratosis	Pitting
Onycholysis	Nail crumbling

Onycholysis is a lifting up or separation of the nail plate from the nail bed. It may be visibly separated, or otherwise may be noted by a well demarcated area extending up from the nail tip a variable distance, where the nail appears as pale or yellow in place of the usual colour.

Oil drop discolouration appears as clearly demarcated discoloured patches within the nail, usually pale or yellow but they may be brown. They are thought to be a localised form of onycholysis; separation of the nail plate from the nail bed, with a build up of air, cells and fluid within.

Splinter haemorrhages appear as narrow linear dark abnormalities, typically towards the tip of the nail. They can occur secondary to trauma, and also occur in other medical disorders including endocarditis and systemic vasculitis. They are thought to represent blood from tiny bleeds between the nail plate and bed, which track up and down linear grooves in the nail bed.

Subungual hyperkeratosis is thickening of the nail bed, thought to represent psoriatic plaques under the nail, where the proliferating cells are unable to desquamate and therefore build up as a thick collection. Red spots may appear in the lunula when inflammation occurs within the nail matrix (Jiaravuthisan et al. 2007).

Pitting is seen as tiny localised superficial depressions within the nail plate. They may occur in clusters or in a linear pattern, longitudinally along the

nail. They are thought to originate in a psoriatic lesion in the nail matrix; defective keratinisation occurs and then as the nail grows, the more superficial cells slough off leaving a depression (Zaias 1990). Nail crumbling resembles pitting on a larger scale, where the production of the nail plate is defective, the nail is therefore fragile and may disintegrate.

Leuconychia appears as bright white patches within the nail. It is fairly common in healthy subjects. It is an abnormality within the nail plate itself, which may reflect calcification.

Figure 4. Nail plate lesions

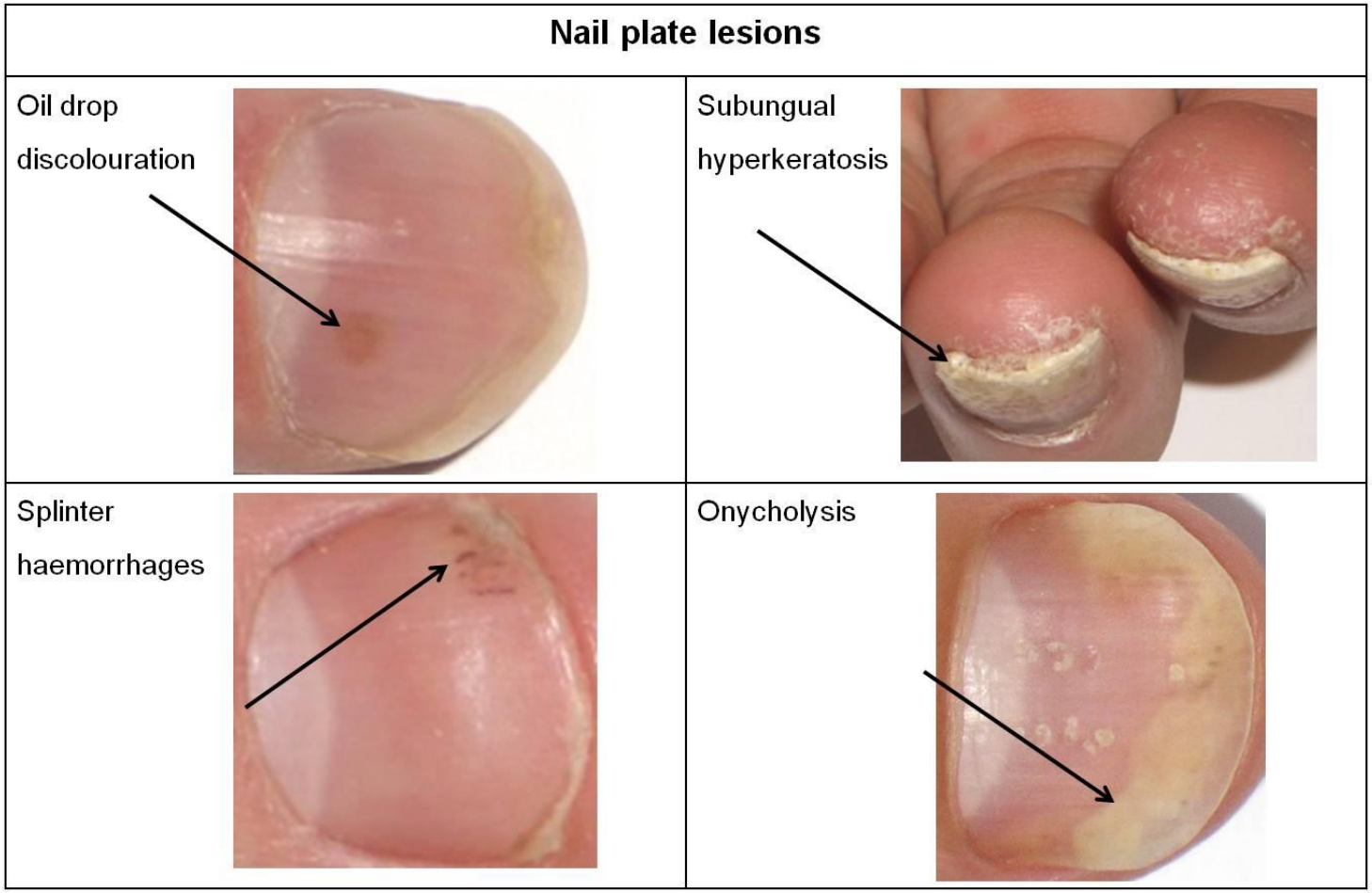
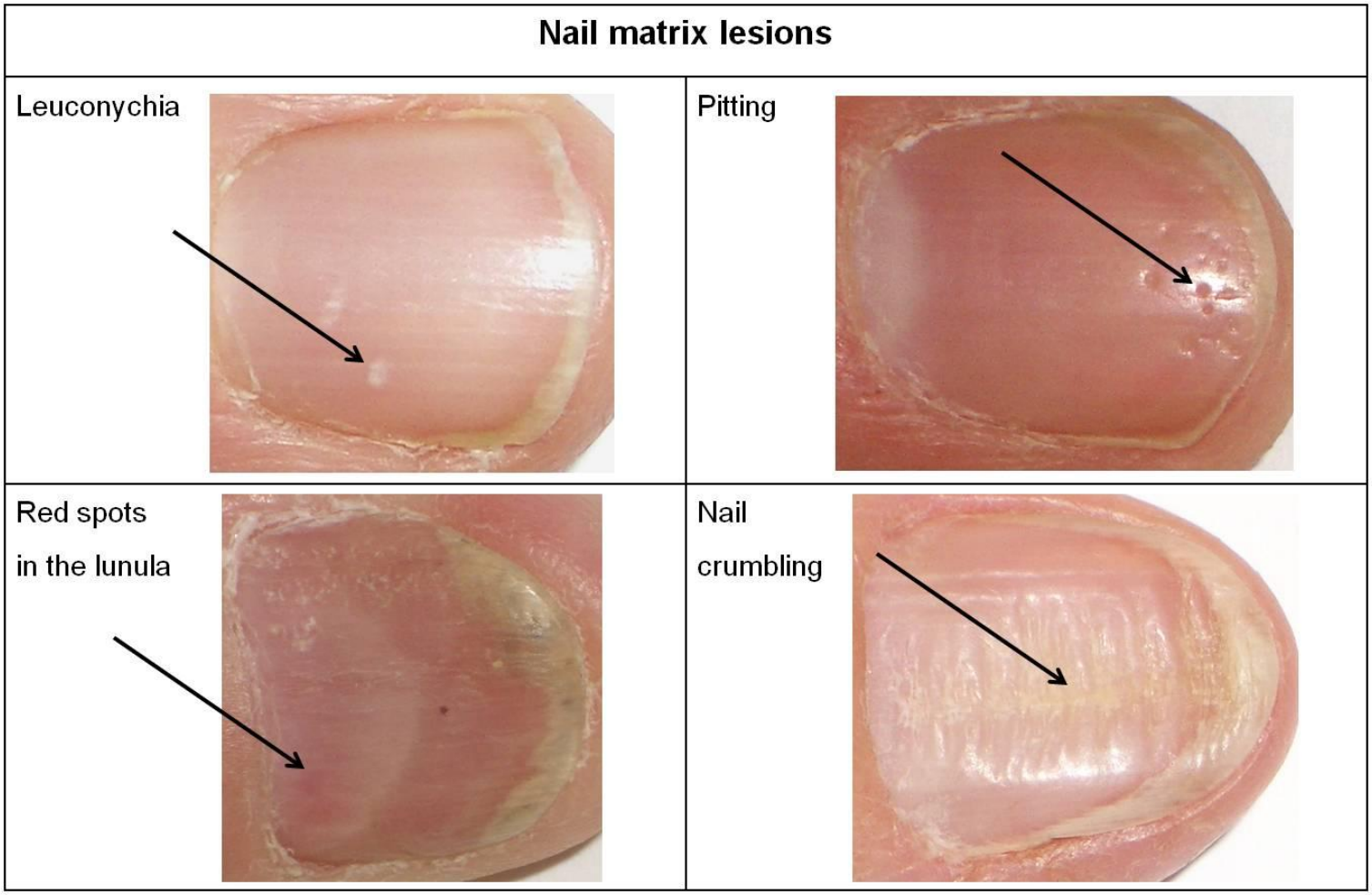


Figure 5. Nail matrix lesions



Some of these abnormalities may also be found in healthy individuals without psoriasis. One small study found pitting and splinter haemorrhages in more than half the healthy subjects, although few had more than two of either feature (Robertson et al. 1974). Leuconychia was also seen very frequently. A study by Verna Wright compared the changes seen in psoriatic patients to those in other medical inpatients in order to assess the discriminative power for a diagnosis of psoriatic nail disease (Eastmond et al. 1979). They reported five conclusions. Onycholysis (in the absence of a history of trauma) suggested a psoriatic cause. The presence of at least two features from onycholysis, horizontal ridging and nail pitting in the same patient suggest a psoriatic cause. The presence of nail pitting alone is not sufficient for the nail disease to be attributed to psoriasis. The presence of more than twenty pits is suggesting of a psoriatic cause, and more than sixty are unlikely to be seen in a non-psoriatic cause.

In a cross-sectional study in Singapore, pitting and onycholysis were the most common abnormalities seen in their psoriasis patients (Tham et al. 1988). This was replicated in a cross-sectional study in Italy (Brazzelli et al. 2012) and was also stated in one of the original papers by Wright (Eastmond et al. 1979).

Recently it has emerged that the nail is functionally integrated into the enthesis network around the DIP joint (McGonagle 2009). This offers a novel explanation for the link between arthritis and skin disease. It also raises the possibility that nail pain in psoriasis without arthritis is in fact a manifestation of enthesitis (see section 2.5.5.1 for further details).

A small case control study comparing psoriasis patients and controls, without diabetes, hypertension or a smoking history assessed the nailfold vessel resistance index (NVRI) in the proximal nail plate using Doppler ultrasound (Husein El-Ahmed et al. 2012). The patients were receiving a variety of systemic therapies for their psoriasis. Sixteen out of 23 psoriasis patients had nail disease. A significant increase in the NVRI was seen in the psoriasis patients with nail disease, compared to those without nail disease and compared to controls also. The authors suggest that this may relate to microvascular changes and endothelial dysfunction involved in the

pathogenesis of psoriasis itself, and the nail changes. One group were able to describe a typical pattern of changes seen on capillaroscopy in psoriasis patients, and the presence of this pattern correlated with the presence of periungual psoriatic lesions, onycholysis and pitting (Ohtsuka et al. 1994). An later assessment of nail fold capillaroscopy in patients with psoriasis and PsA was not able to replicate this but did find reduced capillary bed density in patients with either nail disease or DIP arthritis compared to controls, suggesting a possible role of microvascular disease in the pathogenesis (Bhushan et al. 2000).

The presence of the HLA-Cw*0602 allele differentiates different subtypes of psoriasis, with nail disease being more common in patients who are HLA-Cw*0602 negative (Gudjonsson et al. 2006).

Alterations of the microenvironment of the nail by psoriatic nail disease may also predispose to co-existent fungal nail disease, which can be seen in around half of the psoriatic nails (Natarajan et al. 2010). This may reduce the accuracy of clinical assessment of the nails, particularly the toenails.

2.5.3 Burden of disease

One of the first descriptions of the impact of psoriatic nail disease was by de Jong (de Jong et al. 1996). In a large postal questionnaire study, 1728 patients were surveyed regarding their psoriasis. Nail pain was reported by 51.8% patients and cosmetic problems by 93.3%. Functional impact was also commonly reported; 59% in activities of daily living, 56% for housekeeping and 48% for carrying out their work. Major restrictions at work were reported by 14% patients.

A large cross-sectional study in Germany found that psoriasis patients with nail disease had higher DLQI scores and required more time off work than those with normal nails (Augustin et al. 2010). However, a number of confounding factors may be influencing these results, as patients with nail disease also had higher PASI scores, were more likely to have had inpatient treatment and were more likely to have co-existent PsA. These results were echoed in a later German study (Radtke et al. 2011). Patients with nail

disease had a higher DLQI score and poorer general health as measured by the EQ5-D visual analogue score. Satisfaction with treatment was lower and patients required more time off work.

A retrospective study in France found that the presence of nail disease in psoriasis patients was associated with a higher DLQI score, suggesting again that nail disease does have an impact on quality of life (Lin et al. 2011). In another cohort, a correlation was seen between nail disease severity (measured using the psoriasis nail severity score [PNSS]) and functional impairment (measured using the HAQ), also with anxiety and depression scores (measured using the Hospital Anxiety and Depression Scale) (Williamson et al. 2004a). In contrast, a Japanese study was not able to show a correlation between the mNAPSI score and the HAQ (Japanese version) (Maejima et al. 2010). This may reflect the fact the HAQ is not specific enough for the impact of nail psoriasis.

There is currently only one assessment tool designed to measure the effect of nail disease on quality of life, the nail psoriasis quality of life scale (NPQ10), which was developed and validated in France (Ortonne et al. 2010). This awaits further validation in a longitudinal study to assess the response to change. In the development study, members of a French psoriasis patient organisation were surveyed. 86% of the patients were troubled by their nail disease, 87% felt that it was unsightly and 59% found it painful. The greater the number of involved nails, the more functional, aesthetic and pain impact was seen. Confirming the validity of the score, a correlation between the DLQI and the NPQ10 was seen. Patients with nail disease of both the hands and feet had higher NPQ10 scores than those with it only affecting either the hands or feet.

One open label study has shown an improvement in nail related quality of life in psoriasis patients treated with ustekinumab (Rigopoulos et al. 2011), although this was done using a questionnaire designed for the assessment of quality of life in fungal nail disease (Drake et al. 1999). A study using topical ciclosporin found an improvement in the Psoriasis Disability Index scores in those patients who had complete resolution of their nail disease with treatment (Abe et al. 2011).

2.5.4 Clinical assessment

One of the difficulties, as with the assessment of PsA overall, is developing a scoring system that does not take too much time, but that includes the different facets of nail disease in order to study what potentially may be the result of different pathological processes and may respond to treatment in different ways.

Various options have been developed for the clinical assessment of nail disease. While some studies have used self-reported presence of nail disease, other simple options include a clinician assessment of the presence or absence of nail disease, or the recording of the number of nails affected.

The first formal scoring system was developed in Bath and adapted by a group in Oxford as the psoriasis nail severity score (PNSS), scoring one point per finger nail for the presence each of pitting, onycholysis, hyperkeratosis and dystrophy, giving a total possible score of 40 (or 80 if including the toenails) (Jones et al. 1994; Williamson et al. 2004a).

The Nail Psoriasis Severity Index (NAPSI) is the most frequently used semi-objective measure and was developed by dermatologists in 2003 (Rich et al. 2003). In this method, each nail is divided into four quadrants and the abnormalities scored for each quadrant, with one point for any features of nail bed psoriasis (onycholysis, oil drop spots, splinter haemorrhages and nail bed hyperkeratosis) and one point for any features of nail matrix psoriasis (pitting, leuconychia, red spots in the lunula and nail plate crumbling). This gives a possible score of 2 per quadrant, 8 per nail and thus a total possible score of 80 (or if including the toenails also, a maximum of 160). In this method, individual features do not need to be scored, but it does allow for differentiation between the presence of nail bed and nail matrix features. Initial assessment among dermatologists showed reasonable reproducibility amongst assessors (Rich et al. 2003) and good inter-observer agreement was confirmed in another study (Aktan et al. 2007). The NAPSI has since been used in clinical trials (Kavanaugh et al. 2009; Van den Bosch et al. 2010; Igarashi et al. 2012). However, further studies have shown low intra-reader reliability when used by untrained rheumatologists (Lubrano et al. 2012). The NAPSI, like all currently

available clinical nail severity assessment tools, does not assess quality of life. A target nail NAPSI has also been suggested, where the presence of each feature was scored in each quadrant, giving a maximum score of 32 (Rich et al. 2003). The target NAPSI, and indeed the NAPSI may not be adequately sensitive to change for use in clinical trials as it merely records the presence or absence of features in each quadrant (Parrish et al. 2005). Even if the number of pits or the extent of onycholysis improves, the score will not change unless there is complete resolution within that quadrant.

A modification to the NAPSI (the modified Nail Psoriasis Severity Index, mNAPSI) was then developed (Cassell et al. 2007). This was developed by a group of physicians scoring a set of nail photographs using the NAPSI, and then adapting the system to improve aspects that caused variability between raters. The division of the nail into quadrants was removed and instead, pitting, crumbling were scored on a scale from 0-3. Oil drop discolouration and onycholysis were also combined, as they were felt to represent the same pathology. In the newly modified method, each fingernail is scored for the presence and the severity of pitting, onycholysis and nail plate crumbling (score 0-3) and the presence or absence of splinter haemorrhages, leuconychia, red spots in the lunula and nail bed hyperkeratosis (score 1 for each if present). This gives a total possible score of 140. Validation as part of the original study found excellent inter-rater reliability, along with good correlation with a physician nail VAS and good intra-rater reliability (Cassell et al. 2007). A further international reliability exercise involving both rheumatologists and dermatologists found excellent agreement between raters with the mNAPSI (Chandran et al. 2009). The limitation of the mNAPSI is the time it takes to perform, particularly in patients with severe nail disease.

Robert Baran has also proposed a scoring system for nail psoriasis (Baran 2004). This was created to include nail features that may account for different sites of pathology. This system scores both the fingernails and toenails. A semiquantitative score (0-3) is recorded each for pitting, Beau's lines (transverse grooves), subungual hyperkeratosis (graded using a calliper), onycholysis, trachyonychia, leuconychia and oil drop spots.

Splinter haemorrhages and nail loss are not included in the score. This has not been widely used.

A simple more qualitative scoring system was described by Cannavo as part of an RCT (Cannavo et al. 2003). In this method, a semiquantitative score (0-3) is recorded each for pitting, onycholysis, nail plate crumbling, nail bed hyperkeratosis and oil drop discolouration. The overall score is simply the average of the score for all diseased nails.

A study comparing the NAPSI and Cannavo's scoring system found good inter-rater agreement for the NAPSI, and a good correlation between the two systems. The authors did not find agreement between two raters for the scores in the toenails, which may be more subject to trauma or fungal disease.

2.5.5 Imaging of nails in psoriatic disease (psoriatic arthritis and psoriasis)

2.5.5.1 Magnetic resonance imaging

While conventional radiographs are a useful way to assess the bony structures of the hand, they are limited by the two dimensional nature of the technology, as well as their inability to assess the soft tissues. MRI has therefore been receiving increasing interest as a way to image the nail and the surrounding structures. It allows the study of inflammation within the soft tissues and bone, as well as detecting disease at an earlier stage than is seen on radiographs. High field machines may require uncomfortable positions to be held for some time, and therefore low field extremity machines have been developed which may offer some advantages, but perhaps with loss of some image quality (Soscia et al. 2009).

A series of papers were published by Tan describing the findings on MRI of the finger joints in patients with PsA, OA and healthy controls. In one study of patients with osteoarthritis, either the DIP or PIP joint was imaged (Tan et al. 2005). Cartilage loss, synovitis, osteophytosis and bone marrow oedema were seen. Thickening of the collateral ligaments was noted in every case, but milder changes in the collateral ligaments were also seen in older normal

controls, and in asymptomatic joints in patients with OA elsewhere. In a study comparing DIP joints in OA and PsA patients, the PsA patients generally had a pattern of extracapular changes, entheseal disease, enhancement of the ligaments and more diffuse bone oedema (Tan et al. 2006a). The OA patients did have changes within the ligaments and entheses, but with less inflammation. The diffuse inflammation seen in the PsA patients extended to involve the nail bed. The close association between the nail and the DIP entheses was then examined using cadaveric histological sections, and compared to MRI findings in patients (Tan et al. 2007). Fibres were seen extending from the extensor tendon towards the nail bed on MR. The nail thickness as seen on MR was greater in PsA patients than OA or controls. Using the histological sections, it was confirmed that some fibres from the extensor tendon do continue up to and surround the nail root and matrix. Some fibres from the flexor tendon also anchor the nail root and matrix at the outer aspects. Thereby the diffuse inflammation seen in these areas in PsA may potentially explain the links with nail disease. A previous dissection study had found close links between the collateral ligaments and the lunula and nail matrix (Guero et al. 1994).

Scarpa described methodology to assess the nail and the DIP joint using MRI, with a 1.5 Tesla scanner, a surface coil and with Vaseline applied to the outer surface of the nail in order to visualise the nail thickness (Scarpa et al. 2006b). Twenty three PsA patients with a median NAPSI score of 5 were scanned. Thickening of the nail, with surface irregularity in some, was seen in 95.7% of the patients (100% of those with nail disease) and they recorded a higher MRI nail involvement score in those with nail disease than those without. They did not detect abnormalities in the controls. Within the distal phalanx, 95.7% PsA patients had abnormalities, which were more marked in those patients with clinical nail disease (of whom 100% had abnormailities). Only one control had evidence of bone resorption. Involvement of the DIP joint was again more common in patients with nail disease. No cases had isolated DIP joint involvement without bony changes in the distal phalanx, and the authors suggest that therefore DIP joint involvement is secondary to nail and distal phalanx disease.

McQueen's group have used MRI to assess a cohort of 34 PsA patients with a baseline clinical asessment and MRI, followed by a clinical assessment in 20 patients one year later (Dalbeth et al. 2012). The MRI scan was performed of the dominant wrist and hand, using a 1.5 Tesla scanner with a dedicated wrist coil. At baseline, nail pitting was not associated with MRI changes in the distal phalanx, but onycholysis and hyperkeratosis were. Bone marrow oedema on the baseline MRI was associated with the development of new onycholysis and hyperkeratosis at the one year visit. No comment was made on the nail appearances by MRI. This study is interesting as the results conflict with the traditional thoughts that onycholysis and hyperkeratosis are nail bed lesions and therefore perhaps due to localised psoriasis in the nail bed rather than underlying bone or entheseal disease.

No studies have yet been published describing the MRI findings of nail disease in psoriasis patients.

2.5.5.2 Ultrasound

Two observational studies have studied the ability of ultrasound to image the nails in psoriasis. Gutierrez et al. scanned the skin and nails of 30 psoriasis patients and 15 healthy controls and demonstrated structural changes in the nail and nail bed (focal hyperechoic deposits in the ventral nail plate, loss of definition of the nail plate, a wavy deformity of the nail plate, thickening of the nail bed and increased blood flow seen with power Doppler) (Gutierrez et al. 2009). However, another observational study measuring nail volumes and matrix volumes was unable to detect a difference between healthy controls and patients with psoriatic nail disease (Wollina et al. 2001).

In a cohort of psoriasis and PsA patients, an increased thickness of the nail plate and nail bed was seen in the psoriasis patients with nail disease, compared to healthy controls (Gisondi et al. 2012). A correlation was also seen between the NAPSI score and the nail thickness. Even in the psoriasis patients with clinically normal nails, an increased thickness of the nail plate and nail bed was also seen, when compared to controls.

Gutierrez found abnormalities of the nail plate and bed by ultrasound in PsA patients, with loss of definition of the ventral nail plate in early or mild nail disease and loss of the complete trilaminar appearance in later stages (Gutierrez et al. 2010). Thickening of the nail bed was also seen, as was abnormally increased blood flow in the nail bed in the presence of nail disease. In another study, Gutierrez demonstrated reductions in PD scores in the nail bed with TNF inhibitor treatment (Gutierrez et al. 2012).

2.5.5.3 Optical coherence tomography

Optical coherence tomography (OCT) is a newer imaging technique finding increasing use in the dermatology setting (Welzel et al. 1997). OCT uses infrared light in the same manner that ultrasound uses acoustic waves. The reflections of the light are detected and processed by a computer, generating an image. The axial resolution is 1 – 2mm, and is determined by the bandwidth of the light source. It is therefore only suitable for the assessment of very superficial structures. Within dermatology, it has found use in the assessment of skin cancer, and in opthalmology for retinal assessment (Sakata et al. 2009; Geitzenauer et al. 2011; Pomerantz et al. 2011; Coleman et al. 2013). Initial reports in the assessment of nail diseases using OCT have shown an ability to objectively measure the nail thickness, and demonstrate abnormalities within the nail plate in leuconychia (Mogensen et al. 2007; Abuzahra et al. 2010; Sattler et al. 2012)). Our group has demonstrated the ability of OCT to detect psoriatic nail disease in one case (Aydin et al. 2011) and work is ongoing in a larger cohort.

2.5.6 The response of nail disease to treatment

Historically, the treatment of psoriatic nail disease has been difficult. Research into efficacy may also previously have been hampered by the lack of validated outcome measures.

Topical treatments are commonly used, but require frequent applications for a prolonged period of time, and with little available evidence to support their

efficacy. Most frequently used are glucocorticoids and vitamin D3 analogues, both of which have more data available to support their effectiveness on the skin than the nails. A comparison study of calcipotriol and betamethasone topical treatments for nail psoriasis found around 50% reductions in subungual hyperkeratosis with either treatment (Tosti et al. 1998). Small studies are also available for topical fluorouracil, 5-FU, anthralin, ciclosporin and tazarotene (Jiaravuthisan et al. 2007).

Glucocorticoid injections may also be used, injecting the steroid into or around the nail matrix. Again only small studies are available, with variable results. Injections appear more effective in the treatment of nail matrix lesions (pitting, nail crumbling) than nail bed lesions (such as onycholysis) (Jiaravuthisan et al. 2007). Repeated injections may be needed, the injections can be fiddly, and they may also be painful.

Only two studies have been published describing the effects of PUVA (psoralen plus ultraviolet A light phototherapy) in nail psoriasis. Greater responses were seen for onycholysis than for pitting (Marx et al. 1980; Handfield-Jones et al. 1987).

Two open label studies have demonstrated improvements in nail psoriasis with oral ciclosporin, which is commonly used for skin psoriasis (Mahrle et al. 1995; Feliciani et al. 2004). An open label study comparing methotrexate and ciclosporin found mean reductions in the NAPSI score of 43% and 37% respectively (Gumusel et al. 2011). Acitretin has shown some promise in an open label study of psoriasis patients treated for six months (Tosti et al. 2009). The mean NAPSI was seen to reduce by 41% with treatment, and the mean mNAPSI by 50%. Improvements in the nail disease were seen in 83% patients.

With the advent of the biological treatments for psoriasis and PsA came the realisation that nail disease also improved. Efficacy has been shown for adalimumab, etanercept, golimumab, infliximab, ustekinumab and variably for alefacept (which has since been withdrawn). Initial publications were in the form of case reports and small case series but subsequently as RCTs (although generally as secondary outcome measures and thus without statistical power).

An open label uncontrolled study of adalimumab in PsA included 442 patients, of whom 259 (59%) had nail disease at baseline (Van den Bosch et al. 2010). When assessing the 164 patients with a baseline NAPSI of ≥10, 54% had a ≥50% improvement in the NAPSI at week 12. A small open label study of patients with nail disease and either psoriasis or PsA found a reduction in the mean NAPSI for the fingernails with adalimumab from 10.57 to 1.57 for the psoriasis patients (n=7) and 23.86 to 3.23 for the PsA patients (n=14) (Rigopoulos et al. 2010).

An open label study in patients with nail psoriasis compared etanercept 50mg twice a week to etanercept 50mg once a week for 12 weeks, followed by 12 weeks where both groups received treatment once a week (Ortonne et al. 2013). No significant difference in efficacy was seen between the two groups, with a mean target finger NAPSI score reduction at 24 weeks of 4.3 in the twice a week group, and 4.4 in the once a week group. With baseline mean target nail NAPSI scores of 6.0 and 5.8, the reductions seen are impressive. A large randomised open label study treated psoriasis patients either continuously or intermittently (treated until target reached and then discontinued until flare) with etanercept (Luger et al. 2009). The study included 564 patients with nail psoriasis, with a mean target finger NAPSI of 4.64 at baseline. At 12 weeks, the mean target finger NAPSI was 3.30, at week 54 it was 2.26, with 30% patients having complete clearance in the target nail.

A phase III RCT of golimumab in PsA found significant reductions in the severity of nail disease at both 14 and 24 weeks with golimumab using the physician global assessment of nail disease and the target nail NAPSI (Kavanaugh et al. 2009).

A phase III study of infliximab in psoriasis found statistically significant mean reductions in the NAPSI compared to placebo at as early as ten weeks, with a mean 56% improvement in the NAPSI by 24 weeks (Reich et al. 2005). A further phase III study in psoriasis found complete nail disease clearance in the target nail in 26% patients on infliximab at week 24 (compared to 5% patients on placebo) and in 45% at one year (Rich et al. 2008).

Improvements were seen in both nail bed and nail matrix features of psoriasis

An open label study of 27 psoriasis patients treated with ustekinumab found significant reductions in the NAPSI score at as early as four weeks, and maintained up to 40 weeks (Rigopoulos et al. 2011). A small open label study (n=8) with alefacept showed variable results, with improvement in some patients but worsening in others (Korver et al. 2006).

These studies confirm good responses of nail disease to treatment with an TNF inhibitor, but of course these treatments are expensive and have potential side effects. Treatment guidelines do not currently recommend biologic treatment purely for psoriatic nail disease in the absence of significant skin psoriasis or arthritis (Ritchlin et al. 2009; Gossec et al. 2012).

2.6 Treatment of psoriatic arthritis

Many of the treatments used for psoriatic arthritis are taken from those used for RA. Traditional treatments include non-steroidal anti-inflammatory drugs and a range of 'disease modifying drugs' including methotrexate, sulphasalazine, leflunomide and ciclosporin. However, there are very little good quality RCT data available to provide an evidence base in support of these treatments (Ash et al. 2012a).

2.6.1 Treatment of psoriatic arthritis with biological agents

A systematic literature review and meta-analysis on the pharmacologic treatment of PsA was performed to inform a European League Against Rheumatism (EULAR) taskforce producing new management guidelines (Gossec et al. 2012). The previous guidelines published on the management of PsA were produced by GRAPPA, based on literature reviews performed in 2005 (Ritchlin et al. 2009). Given a significant body of

new data available since then, it was felt appropriate to produce new guidelines.

Systematic literature searches covering the period between 1962 to January 2010 were performed using PubMed MEDLINE, EMBASE and COCHRANE databases, to identify all articles reporting the efficacy and safety of biological agents in PsA (Ash et al. 2012a).

The taskforce was responsible for outlining the scope of the literature search, specifying research questions designed to facilitate the formulation of the guidelines and evaluating the results of the systematic literature search.

Inclusion criteria for this review were: (1) systematic reviews and meta-analyses; (2) double-blind randomised controlled trials (RCTs); (3) patients with PsA; (4) studies involving biological agents; (5) studies recruiting at least five patients; (6) publications in English, French, German, Italian or Spanish. With regard to biological agents, data on safety and efficacy were extracted from all studies, but only double-blind RCTs were included in the meta-analysis. Data were extracted from the articles independently by two reviewers. Discrepancies were resolved by discussion.

Where possible (in particular for biologics), efficacy data were meta-analysed using Revman V.5.0. software and expressed as RR for dichotomous variables or mean differences for continuous variables. Random effects were assumed throughout and heterogeneity was assessed using the χ^2 test and I^2 test. Where the heterogeneity test was significant at $p<0.1$, data were not pooled. Toxicity data from RCTs were meta-analysed using generic inverse variance analysis of the natural log of the rate ratio (of events per 100 patient years, random effects assumed).

2.6.1.1 The efficacy of biological treatments

Of 1974 articles screened, 132 articles and 33 abstracts were included in the final review. These included 11 RCTs used for the efficacy meta-analysis on adalimumab, alefacept, efalizumab, etanercept, golimumab, infliximab and

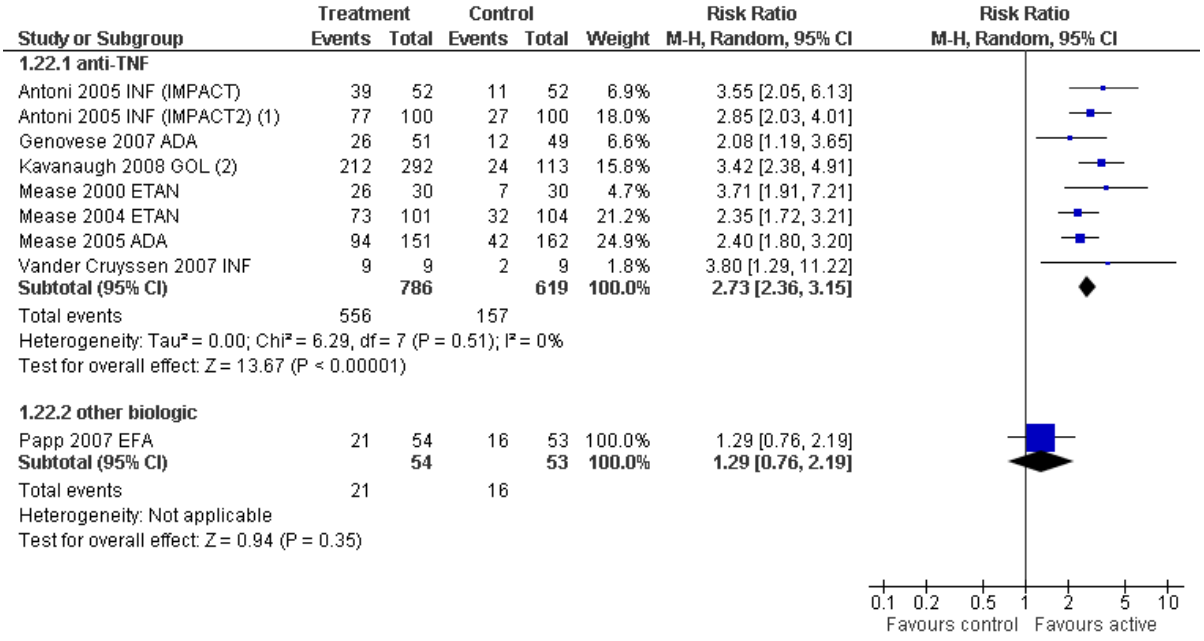
ustekinumab. Results are summarised according to questions formulated by the EULAR taskforce.

a) In patients with PsA, is treatment with biological agents efficacious compared to placebo or active comparator?

All TNF inhibitors (adalimumab, etanercept, golimumab and infliximab) showed efficacy at 12 – 16 weeks for Psoriatic Arthritis Response Criteria (PsARC) response, American College of Rheumatology (ACR) 20, 50 and 70 response criteria and Psoriasis Area and Severity Index (PASI) (Mease et al. 2000; Mease et al. 2004; Antoni et al. 2005a; Antoni et al. 2005b; Mease et al. 2005; Genovese et al. 2007; Vander Cruyssen et al. 2007; Kavanaugh et al. 2009) (Figure 6). Efalizumab was not superior to placebo for PsARC response or ACR 20, 50 and 70 responses (Papp et al. 2007). Ustekinumab was superior to placebo in achieving ACR 20 and 50 responses (Gottlieb et al. 2009).

Figure 6. Efficacy of biological drugs in PsA

Risk ratios for PsARC response at 12 - 14 weeks comparing the use of a biological disease modifying antirheumatic drug versus placebo in patients with psoriatic arthritis



(1) 14 weeks
(2) 14 weeks

Improvements in Health Assessment Questionnaire (HAQ) were greater with adalimumab (Mease et al. 2005; Genovese et al. 2007), infliximab (Antoni et al. 2005a; Antoni et al. 2005b), ustekinumab (Gottlieb et al. 2008) and alefacept (Mease et al. 2006a) than placebo at 12 weeks, and with adalimumab (Mease et al. 2005), etanercept (Mease et al. 2004), golimumab (Kavanaugh et al. 2009) and infliximab (Antoni et al. 2005a) at 24 weeks, but not with alefacept (Mease et al. 2006a) at 24 weeks. Radiographic progression as measured by the modified total Sharp or PsA modified van der Heijde Sharp scoring method was lower for patients treated with etanercept (Mease et al. 2004), golimumab (Kavanaugh et al. 2012a) and infliximab (van der Heijde et al. 2007) at 12 months compared to placebo. Data for adalimumab (Gladman et al. 2007b) and infliximab (Kavanaugh et al. 2006) showed significant differences compared to placebo at 24 weeks.

b) Is there a different efficacy of biological agents in PsA subtypes of articular involvement (monoarthritis, oligoarthritis, polyarthritis, axial disease, dactylitis, enthesitis)?

For peripheral joint disease, no RCTs reported results separately for the different subtypes of PsA. With regards to spinal disease, only one observational study (Olivieri et al. 2008) was found reporting on spinal disease associated with PsA although final results were pooled for patients with and without spinal disease.

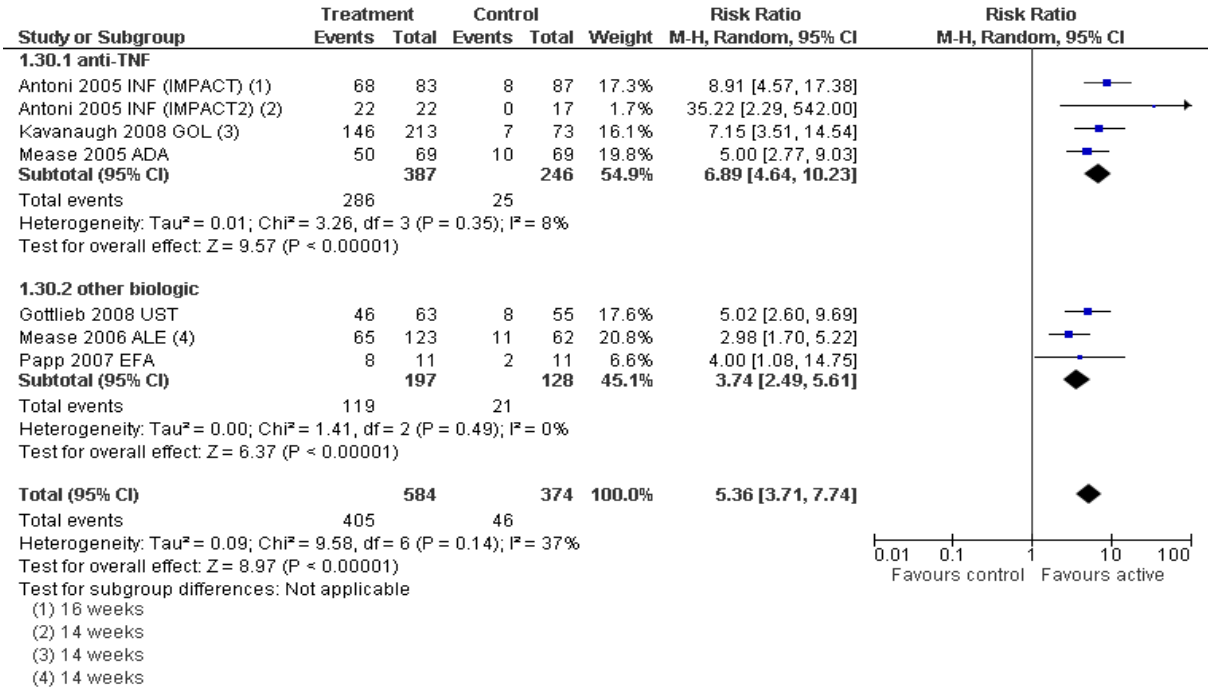
For dactylitis and enthesitis, six RCTs reported data (between 12 - 16 weeks) (Antoni et al. 2005a; Antoni et al. 2005b; Genovese et al. 2007; Gottlieb et al. 2009; Kavanaugh et al. 2009; Sterry et al. 2010) showing significant benefits with golimumab, infliximab and ustekinumab. However both (dactylitis and enthesitis) were reported as secondary outcomes with no prior power calculations having been performed. Studies used different outcome measures with only a proportion of patients having documented baseline dactylitis or enthesitis.

c) Is there efficacy of biological agents on the extra-articular manifestations of PsA (ie: skin and nail involvement)?

Skin disease: Nine RCTs reported data for PASI responses. Treatment with all TNF inhibitors was better than placebo at reducing the PASI score at both 12 and 24 weeks (Mease et al. 2000; Mease et al. 2004; Antoni et al. 2005a; Antoni et al. 2005b; Mease et al. 2005; Kavanaugh et al. 2008) (Figure 7). Efficacy was also demonstrated for alefacept, efalizumab and ustekinumab (Papp et al. 2007; Gottlieb et al. 2008; Mease et al. 2009).

Figure 7. Efficacy of biological drugs for psoriasis

Risk ratios for PASI 50 response at 12 - 16 weeks comparing the use of a biological disease modifying antirheumatic drug versus placebo in patients with psoriatic arthritis



Nail disease: Only one RCT reported on nail disease. Patients treated with golimumab showed a significantly greater percentage change in Nail Psoriasis Severity Index (NAPSI) score at both 14 and 24 weeks (Kavanaugh et al. 2009). Two large observational studies with adalimumab also showed clear improvements in nail disease (Manger et al. 2008; Van den Bosch et al. 2010).

d) In the treatment of PsA, are there differences in efficacy or safety between the different biological agents (spine, skin, nail etc.)?

There is evidence for a lower RR for etanercept for a PASI 75 response at 12 weeks (11.00, 95% CI 0.65, 186.02) when compared to the other anti-TNF agents. Efficacy of etanercept is demonstrated at 24 weeks, but with a lower RR than adalimumab, golimumab and infliximab.

e) In TNF-blocker inadequate responders, what evidence is there for efficacy of a second biological agent?

While no RCTs are available, data from observational studies were available from 8 scientific papers (Gomez-Reino et al. 2006; Conti et al. 2007; Descalzo et al. 2007; Papoutsaki et al. 2007; Pitarch et al. 2007; Coates et al. 2008b; Mazzotta et al. 2009; Saad et al. 2009) and one abstract (Burmester et al. 2008). Data from the Spanish registry BIOBADASER show drug survival of 0.87 (95% CI 0.83 – 0.90) for the first biologic and 0.81 (95% CI 0.65 – 0.90) for the second biologic, although numbers are small (Gomez-Reino et al. 2006). A later publication from BIOBADASER (Descalzo et al. 2007) reported that 23 of 118 patients had discontinued their second biologic (mean follow up 2.18 years), and 2 of 15 patients had discontinued their third agent. A paper from the British Society for Rheumatology Biologics Register (BSRBR) (Saad et al. 2009) shows one year drug survival of 0.82 (95% CI 0.79 – 0.85) for the first biologic and 0.74 (95% CI 0.71 – 0.78) for the second. Four observational studies also documented good response rates in patients switching to a second agent (Conti et al. 2007; Papoutsaki et al. 2007; Coates et al. 2008b; Mazzotta et al. 2009).

f) Is there evidence of greater efficacy or greater risks with combination therapy (with DMARDs)?

Data available from RCTs are limited. Both IMPACT2 and ADEPT showed similar response rates comparing biologic monotherapy versus combination of a biologic agent with a DMARD (Antoni et al. 2005a; Mease et al. 2005). Seven other papers and one abstract were reviewed. Data from the Norwegian DMARD register showed similar response in patients who received concomitant methotrexate (MTX) compared to those on monotherapy biologic at six months (Heiberg et al. 2007). However, a significantly increased drug survival was seen at one year in those patients receiving combination therapy with MTX and a biologic, compared to

monotherapy biologic (P=0.02) (Heiberg et al. 2008). A further analysis of 440 patients in the NOR-DMARD register found again no difference in treatment response, but greater drug survival in those patients also receiving methotrexate, and this effect was most marked with infliximab (Fagerli et al. 2013). Patients receiving infliximab monotherapy had a greater chance of adverse events leading to treatment discontinuation. Data from the South Swedish Arthritis Treatment Group (SSATG) register also described better drug survival in those patients on concomitant MTX (Hazard Ratio 0.64, 95% CI 0.39 – 0.95, P=0.03), due to fewer drop-outs for adverse events (Kristensen et al. 2008). A further paper published by the same group in 2009 showed an increased risk of dose escalation of infliximab in patients not taking MTX (P=0.03) (Kristensen et al. 2009).

2.7 Arthritis mutilans

Psoriatic arthritis is associated with a number of manifestations. One of these is the development of a very destructive arthritis of the small joints of the hands and feet with extensive dissolution of the bone. This highly osteolytic arthropathy is known as arthritis mutilans and was described by Verna Wright as one of the subtypes of PsA (Wright et al. 1976). Many cases have been reported historically, with a description of the 'opera glass hand' syndrome describing the redundant skin and the ability to manually lengthen the digits (Swezey et al. 1972).

One of the characteristic radiographic features is the pencil-in-cup deformity, resulting from destruction blunting the head of the metacarpal or other bone, and resorption and new bone formation creating a cup at the base of the phalanx (Swezey et al. 1972; Laurent 1985). Even in the same patient the different pathological processes can occur, as is demonstrated in a case with severe erosive disease in the peripheral joints and florid new bone formation in the spine (Ly et al. 2009). An MRI study comparing 11 patients with arthritis mutilans with 17 patients with other forms of erosive PsA found higher MRI erosion, bone proliferation and bone oedema scores in the patients with arthritis mutilans (Tan et al. 2009). The authors suggested that bone oedema could reflect a pre-erosive feature, but this would require clarification in a longitudinal study.

Cross-sectional studies have found arthritis mutilans in 2 - 5% of PsA patients (Torre Alonso et al. 1991; Jones et al. 1994; Veale et al. 1994; Nossent et al. 2009; Reich et al. 2009). One study found no clinical predictors of which patients develop arthritis mutilans and found that it could occur in any PsA subtype (Kammer et al. 1979). A study following 73 patients found a significant association between axial disease and female sex with arthritis mutilans (Marsal et al. 1999). Data from the Classification of Psoriatic ARrthritis (CASPAR) study (Taylor et al. 2006) found that patients with arthritis mutilans had a longer disease duration, more joints involved, were more likely to be ACPA positive, have undergone surgery and

have radiographic damage (Helliwell 2009). A possible definition of arthritis mutilans has been proposed, with criteria including polyarticular disease, a long disease duration, symmetrical arthritis, ACPA positivity and characteristic radiographic features (osteolysis, ankylosis, entheseal abnormalities, and spinal involvement) (Helliwell 2009).

Arthritis mutilans can develop quickly and there is an urgent need to better identify it, so that effective but expensive therapies could be promptly initiated in this disease subgroup.

2.8 Predictors of radiographic progression in psoriatic arthritis

Magnetic resonance imaging of the sacroiliac joint has been used in early axial spondyloarthropathy, which is closely related to PsA, to show that baseline MRI bone oedema, histologically an osteitis, is associated with the development of radiographic destructive changes eight years later (Bennett et al. 2008). However much of the pathology in the sacroiliac joint and the spine is characterised by new bone formation whereas the hand pathology in PsA is typified by joint destruction. In a prospective longitudinal study, inflammation in an individual joint in PsA has been shown to later predict clinical damage to that joint (Cresswell et al. 2011). Radiographic data was not presented. A cross sectional study demonstrated higher levels of bone oedema in arthritis mutilans compared to erosive PsA without bone lysis, with a correlation seen between bone oedema and current radiographic damage (Tan et al. 2009). A small retrospective study found that patients with an increasing swollen joint count developed more radiographic damage than those with a stable or reducing number of swollen joints (Simon et al. 2012). That study also echoed the results of the RCTs, with less radiographic damage occurring in patients receiving TNF inhibitors than in patients on DMARDs. In an analysis of RCT data, achieving the Minimal Disease Activity criteria (Coates et al. 2010a) also led to less radiographic progression (Coates et al. 2010b), supporting the idea that active disease is

a risk factor for ongoing radiographic progression. Data from an adalimumab RCT found the baseline and mean CRP level to be associated with radiographic progression, but again with less progression in those patients treated with the TNF inhibitor compared to those receiving placebo (Gladman et al. 2010). Similarly, data from the Bath cohort show increased radiographic progression with a higher plasma viscosity at baseline (McHugh et al. 2003).

In a cross-sectional study, multivariate analysis found DIP involvement and polyarticular disease to be associated with aggressive joint manifestations such as radiological erosions or irreversible deformities (Alenius et al. 2002a). ACPA antibodies were found to be associated with polyarticular disease but not radiographic damage or clinical deformity (Alenius et al. 2006). However, another small study found an association between ACPA antibodies and erosive disease (Korendowych et al. 2005). A prospective study of 100 PsA patients found an increased risk of destructive arthritis in women, and radiographic changes more frequently in patients with symmetrical arthritis (Kammer et al. 1979). A prospective study of patients with early PsA in Ireland found significantly more periostitis on follow-up radiographs in patients presenting with young onset (age <60) than elderly onset PsA (Kane et al. 2003). Another prospective study comparing young and elderly onset PsA found more aggressive disease in the elderly onset PsA, with higher inflammatory markers and more radiographic progression (Punzi et al. 1999). In another study, axial disease and a history of swollen joints during the follow-up up period were associated with radiographic erosions (Marsal et al. 1999). A retrospective study found an association between female sex and erosive disease (Queiro et al. 2001). A prospective study following 71 patients with PsA found only polyarticular onset of disease to be an independent predictor of the development of erosive and deforming disease, with an odds ratio of 37 (Queiro-Silva et al. 2003). Initial analysis from that study showed the development of erosive disease to be more common in females and those with DIP disease and the HLA B27 genotype. Contrastingly, one of the original studies by Verna Wright's group found more radiographic damage in men (Roberts et al. 1976).

Data from the Toronto PsA cohort which has been ongoing since 1976 has found an association between the development of clinically damaged joints and a higher number of swollen or inflamed joints, raised inflammatory markers, clinically damaged joints at baseline, female sex and the duration of PsA (Gladman et al. 1995; Gladman et al. 1999; Siannis et al. 2006). Gladman has also reported predictors of radiographic damage to include DIP disease, symmetrical polyarthritis, the number of swollen and tender joints at the last visit, age, disease duration, baseline ESR and previous clinical damage (Gladman et al. 1987a; Bond et al. 2007). They have also noted an increase in radiographic damage in a dactylitic compared to non-dactylitic digit (Brockbank et al. 2005).

2.9 Summary

Enthesitis is a characteristic feature of PsA. The nail bed and matrix are closely associated with the entheses of the ligaments and tendons around the DIP joint. In PsA with active arthritis of the DIP joint, there is diffuse inflammation of the bone, soft tissues, and entheses surrounding the nail matrix, and this is associated with the presence of nail disease.

A significant proportion of patients with psoriasis have an underlying subclinical enthesitis seen around the large joints, but the significance of this is not yet known. The role of DIP joint enthesitis in the pathogenesis of nail disease in psoriasis (without arthritis) is not yet known. Clinical predictors for the presence of subclinical enthesitis have not yet been investigated.

Nail disease is known to improve with TNF inhibitor therapy in both psoriasis and PsA. These treatments are also effective for enthesitis.

Arthritis mutilans is a rare subtype of PsA and on a cross-sectional basis is associated with bone oedema. Active arthritis predicts later radiographic damage in the same joint in PsA. Imaging features which predict the later development of arthritis mutilans have not been established.

Chapter 3
Aims and objectives

The hypotheses of this work are that:

1. **Nail disease could be a marker for those psoriasis patients who have subclinical enthesitis elsewhere, and therefore could be a potential predictor for the later development of PsA**

2. **Nail disease is due to subclinical or clinical enthesitis around the DIP joint in both PsA and psoriasis**

3. **The improvement in nail disease seen with anti-tumour necrosis factor (TNF) therapy may be due to improvements in enthesitis around the DIP joint**

4. **DIP joint bone marrow oedema lesions in active PsA are predictive of radiographic damage in that joint at a later stage**

A number of research questions have been formulated based on these hypotheses:

Table 8. Research questions addressed in this thesis

Research Question	**Aim**	**Methodology to answer this**	**Study to address this**	**Chapter**	**Reference if published**
Could nail disease be a marker for those psoriasis patients who have subclinical enthesitis elsewhere, and could this be a potential predictor for the later development of PsA?	To explore whether nail disease in PsA and nail disease in psoriasis but without arthritis points to a systemic polyenthesitis	Cross-sectional observational study	MAP *	Chapter 4 Chapter 5	(Ash et al. 2012b) (Aydin et al. 2013)
Is nail disease due to clinical or subclinical enthesitis around the DIP joint in both PsA and psoriasis?	To describe the pattern of enthesitis around the DIP joint seen on high field magnetic resonance imaging (MRI) in patients with psoriasis and PsA, related to the presence or absence of nail disease	Cross-sectional observational study	MAP *	Chapter 6 Chapter 7	(Aydin et al. 2012)

Research Question	Aim	Methodology to answer this	Study to address this	Chapter	Reference if published
Is the improvement in nail disease seen with anti-tumour necrosis factor (TNF) therapy due to improvements in enthesitis around the DIP joint?	To describe the changes seen in nail disease and DIP enthesitis in patients before and after receiving anti-TNF therapy for psoriasis or psoriatic arthritis	Observational cohort study	NET≈	Chapter 8	
Are DIP joint bone marrow oedema lesions in active PsA predictive of radiographic damage in that joint at a later stage?	To investigate the predictive value of the bone marrow oedema MRI lesion in the DIP joint in PsA in the future development of osteolysis	Long term follow-up of a previous cohort	PAMPA ≈	Chapter 9	

* MAP: High resolution MRI of the nail and ultrasound of Asymptomatic entheses in patients with Psoriasis

≈ NET: High resolution MRI to describe the changes in Nail disease and Enthesitis around the DIP joint in patients with psoriasis and psoriatic arthritis receiving biologic Therapy

≈ PAMPA: The Prognostic value of baseline MRI-determined osteitis in predicting Arthritis Mutilans in Psoriatic Arthritis

Chapter 4
Ultrasound imaging of the peripheral entheses in psoriasis patients

4.1 Introduction

Psoriasis affects approximately 2% of the population and up to 30% of these will develop psoriatic arthritis (PsA) (Gelfand et al. 2005b; Radtke et al. 2009; Reich et al. 2009; Christophers et al. 2010). As dermatologists usually see patients with psoriasis before arthritis develops then they are well placed to diagnose PsA early. Now that effective therapies for the suppression of PsA exist, the early recognition of PsA has important consequences for optimal patient management. Presently, the conceptual basis for the link between psoriasis and nail disease and subsequent PsA is poorly understood.

It has been suggested that enthesitis is the primary lesion that underscores the diverse skeletal manifestations of PsA (McGonagle et al. 1998b). It has also been demonstrated that subclinical enthesopathy and associated osteitis is present in up to 50% of patients with psoriasis with no arthritis (Gisondi et al. 2008; McGonagle et al. 2011a). Another stream of research has shown that the presence of nail disease is a harbinger for the future development of PsA (Wilson et al. 2009a). These findings are noteworthy since it has been shown that psoriatic nail disease in PsA is intimately associated with enthesopathy of the distal interphalangeal joint and that the nail is functionally integrated with the enthesis (Tan et al. 2006a; Tan et al. 2007; McGonagle et al. 2009a).

These combined clinical and imaging observations suggest that there may be a link between systemic enthesopathy and psoriatic nail disease. Therefore, the question is posed here as to whether nail disease in psoriasis is linked to a greater degree of systemic enthesopathy compared to psoriasis patients without nail disease. Such a link would offer a novel

unifying concept for nail disease, systemic enthesopathy and the future development of PsA.

4.2 Methods

The study was carried out in two European populations (Leeds, UK and Verona, Italy). Ethical approval for the study was obtained in both countries.

4.2.1 Patient groups and clinical assessment

Forty-six patients with psoriasis (31 with nail disease) and 21 healthy controls (HC) were included. Thirty-six patients were recruited in the UK, 10 patients and the HC were recruited in Italy. Any patients with PsA according to the CASPAR criteria (Taylor et al. 2006), patients with evidence of osteoarthritis, and those with arthralgia or articular symptoms were excluded. The clinical assessment was performed by a clinician blinded to the US data. The clinical assessment included a PASI and BSA score, tender (78) and swollen (76) joint count, Leeds and SPARCC enthesitis indices and a dactylitis count. Modified NAPSI scores for all fingernails were recorded for patients recruited in UK (Cassell et al. 2007). Patients completed questionnaires including the PEST and DLQI and high resolution photographs of the nails were taken. Patients receiving glucocorticoids and anti-TNF therapies were excluded from the study, those receiving DMARD therapy were recruited if they had active skin disease (inadequate responders).

For HC recruitment, adults aged between 18-64 who were accompanying patients were approached in the outpatient clinical waiting area. People without a history of arthritis and psoriasis were recruited.

4.2.2 Ultrasonography

Ultrasound was performed by three rheumatologists fully trained in musculoskeletal US and with a special interest in scanning enthesitis (SZA and CC-G in UK, IT in Italy) using a Logiq E9 machine in UK and Logiq 5 machine in Italy (General Electric, Wauwatosa, Wisconsin USA) both with a linear probe at 9–14 MHz.

Ultrasound of the lower limbs entheses (Achilles, plantar fascia insertion, quadriceps insertions, patellar tendon origins and insertions) and common extensor tendon origins of the upper limbs was performed blinded to the presence of psoriasis or nail disease. To enable blinding, patients were asked not to communicate with the ultrasonographer about their disease during the US assessment. The sonographer did not perform a physical examination, therefore sites other than those involved in the US scan were not seen by the sonographer. The room was completely darkened starting from the beginning of the US assessment. The light of the US machine alone is not enough for the sonographer to see the nails clearly.

The patients were placed in a supine position to assess the entheses around the knee (extended to assess the presence of Doppler signal and semiflexed to 30 degrees to assess the grey-scale (GS) changes) and in a prone position with the feet over the end of the examination table for visualization of the entheses around the heel. To assess the common extensor tendon, patients were placed in a sitting position with the elbow flexed to 90 degrees (Table 9).

Table 9. Entheseal sites assessed by US, patient and probe positioning

Enthesis	**Position of the patient**	**Probe placement (Longitudinal and transverse)**
Proximal patellar tendon	In supine position with the knee extended to assess the presence of Doppler signal and semiflexed to 30 degrees to assess the grey-scale changes.	Distal pole of the patella
Distal patellar tendon	In supine position with the knee extended to assess the presence of Doppler signal and semiflexed to 30 degrees to assess the grey-scale changes.	Anterior tibial tuberosity
Quadriceps tendon	In supine position with the knee extended to assess the presence of Doppler signal and semiflexed to 30 degrees to assess the grey-scale changes.	Proximal pole of the patella
Achilles tendon	In prone position with the feet over the end of the examination table in neutral position	Dorsal aspect of calcaneus
Plantar fascia	In prone position with the feet over the end of the examination table in neutral position	Plantar aspect of calcaneus
Common extensor tendon	In a sitting position and the elbow flexed to 90 degrees.	Lateral elbow

The PD settings were standardized with a pulse repetition frequency of 750 Hz, a colour-mode frequency of 9.1 MHz and low wall filters. The colour gain was increased to the maximum level not generating PD signals under the bony cortex. All US assessments were performed using a multiplanar scanning technique.

4.2.3 Ultrasound image interpretation

The OMERACT definition of enthesopathy was used to interpret US images: “abnormally hypoechoic (loss of normal fibrillar architecture) and/or thickened tendon or ligament at its bony attachment (may occasionally contain hyperechoic foci consistent with calcification), seen in two perpendicular planes that may exhibit Doppler signal and/or bony changes including enthesophytes, erosions, or irregularity” (Wakefield et al. 2005). Bursal enlargement was also scored. Thickness measurements and erosions were scored quantitatively, except the thickness of the common extensor tendon which was assessed semi-quantitatively. The thickness of the entheses was measured at the level of insertions in longitudinal scans. Normal values for each insertion was accepted as reported in the literature (Balint et al. 2002) and additionally < 1 mm of increase exceeding the threshold was scored as grade 1, ≥1 but <2 mm of increase was scored as grade 2 and ≥2mm was scored as grade 3. Erosions were also scored quantitatively (maximum diameter of the erosion >0, <2 mm: grade 1; ≥2, <3 mm: grade 3; ≥3 mm: grade 3). The rest of the assessments were done on a semiquantitative basis (mild changes grade 1, moderate grade 2 and severe grade 3).

Ultrasound findings were categorized according to the following:

The GS changes related to inflammation (entheseal hypoechogenicity, thickening and bursal enlargement) and the PD scores were added up to create an “inflammation score” (range 0-156). The GS changes related to chronic findings (calcifications, erosions and enthesophytes) were added up to calculate a “chronicity score” (range 0-108). A total score (by adding up all findings) had a possible range of 0-264 (Table 10).

Table 10. Components of the ultrasound enthesitis score, with the maximum possible score per patient

The two bursa scores are not applicable at the proximal patellar tendon insertion or plantar fascia. Each patient is assessed at 12 entheseal sites (six on each side). Each individual enthesis is scored from 0 – 3 for each feature.

Section of score	**Sub-section**	**Feature**	**Maximum possible score per patient**	**Total**
Chronicity score		Calcifications	36	108
		Erosions	36	
		Enthesophytes	36	
Inflammation score	Grey scale inflammation score	Entheseal hypoechogenicity	36	96
		Thickening	36	
		Bursal enlargement	24	
	PD score	PD at the enthesis	36	60
		PD in the bursa	24	
Total inflammation score				156
Total score				264

4.2.4 Statistics

Categorical data are expressed as frequencies, and continuous variables are given as means (standard deviation) or medians (range) (depending on the distribution). The prevalence of each individual lesion by US in patients with or without nail disease was compared by using a chi-square test. Mann-Whitney U test was used in order to compare US scores between groups.

Correlations between clinical parameters (mNAPSI, PASI, and disease duration) and US scores (separately for US scores related to inflammation, damage and total) were analysed by Pearson correlation test. Statistical analysis was performed using SPSS version 11.5.

For agreement between sonographers, all investigators agreed on definitions and the scoring system prior to the study both on saved images and while acquiring sample images. 1020 stored images of 21 patients for

grey scale and PD for all entheses included in the study were scored by all 3 investigators and ICC values were calculated for each pair of investigators.

4.3 Results

4.3.1 Inter-observer agreement

A moderate to excellent agreement between both investigator pairs were calculated for different US scores: for GS inflammation the ICC values were 0.91-0.93 (95% CI: 0.79-0.97), for PD inflammation 0.74-0.95 (95% CI:0.45-0.98), for chronicity scores 0.89-0.93 (95% CI:0.76-0.98) and for total US scores 0.92-0.95 (95% CI:0.81-0.98).

4.3.2 Patient characteristics

The distribution of key characteristics of patients and HCs did not differ significantly [for age mean (SD) 44.2 (15.5) vs 50.5 (10) respectively; p=NS] [for BMI 26.7 (5.1) vs 24.9 (2.7) respectively; p=NS] (female %: 50% in psoriasis vs 52.4 % in HC). Comparing psoriasis patients with nail disease and those with normal nails, again similar values for age and BMI were seen [for age mean (SD) 46.7 (15.9) vs 39 (13.8) respectively] [for BMI 27.4 (5.7) vs 25.6 (3.6)]. PASI scores of psoriasis patients with [5.6 (4.1)] or without nail disease [6.3 (5)] were similar. They also had similar disease durations [19.1 (10) years for nail disease and 14.1 (12.6) years for psoriasis; p=0.06]. Nail findings within the nail disease group were as follows: 104/310 nails had onycholysis 165/310 had pitting and 41/310 had crumbling. Although no patients reported joint symptoms and none had clinically evident joint swelling, 4 cases had mild entheseal tenderness on physical examination (3 with nail disease, 1 without nail disease). Three of these patients had tenderness only at one site (2 lateral epicondyle and 1 patellar ligament insertion) and 1 patient had tenderness at multiple sites.

4.3.3 Soft tissue changes at insertions

Patients with psoriasis had higher inflammation scores than HC [med (range): 12 (0-34) vs. 5 (0-19), p<0.001]. The inflammation scores of psoriasis patients with nail disease [13 (0-34)] were higher than both patients without nail disease [8 (2-15); p=0.02] and HC [5 (0-19), p<0.001] (Figure 8 and 9, Table 11). Hypoechogenicity and thickening were more frequent in patients with nail disease compared to patients without nail disease (Table 12). With a Bonferroni correction, only entheseal thickening remains significantly more frequent in psoriasis patients with nail disease.

Table 11. Median ultrasound scores for psoriasis patients and healthy controls

	Psoriasis patients with nail disease	**Psoriasis patients with normal nails**	**Healthy controls**
Inflammation score	13	8	5
Chronicity score	10	5	7
Total US score	23	15	11

Figure 8: Relationship between ultrasound enthesopathy scores and nail disease

Comparison of median US scores related to inflammation and chronicity in psoriasis patients with and without nail disease and healthy controls.

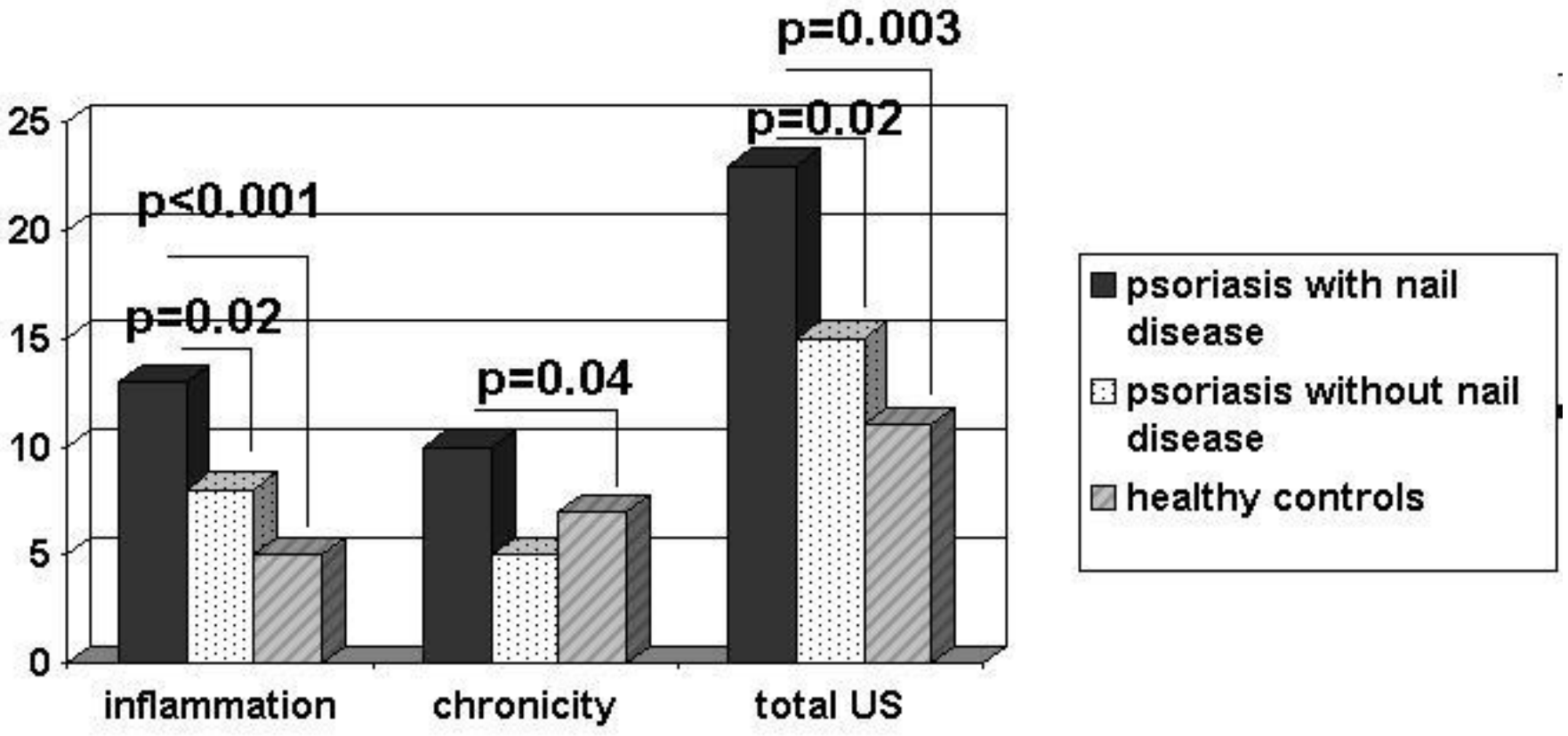


Figure 9: Example nail photograph and ultrasound scan

A. Photograph of thumb nail of a patient with psoriasis, showing onycholysis and an oil drop spot. B. Longitudinal US scan of the proximal insertion of the patellar tendon of the same patient showing severe thickening (white line=0.7 mm), hypoechogenicity (*) and a large enthesophyte (e).

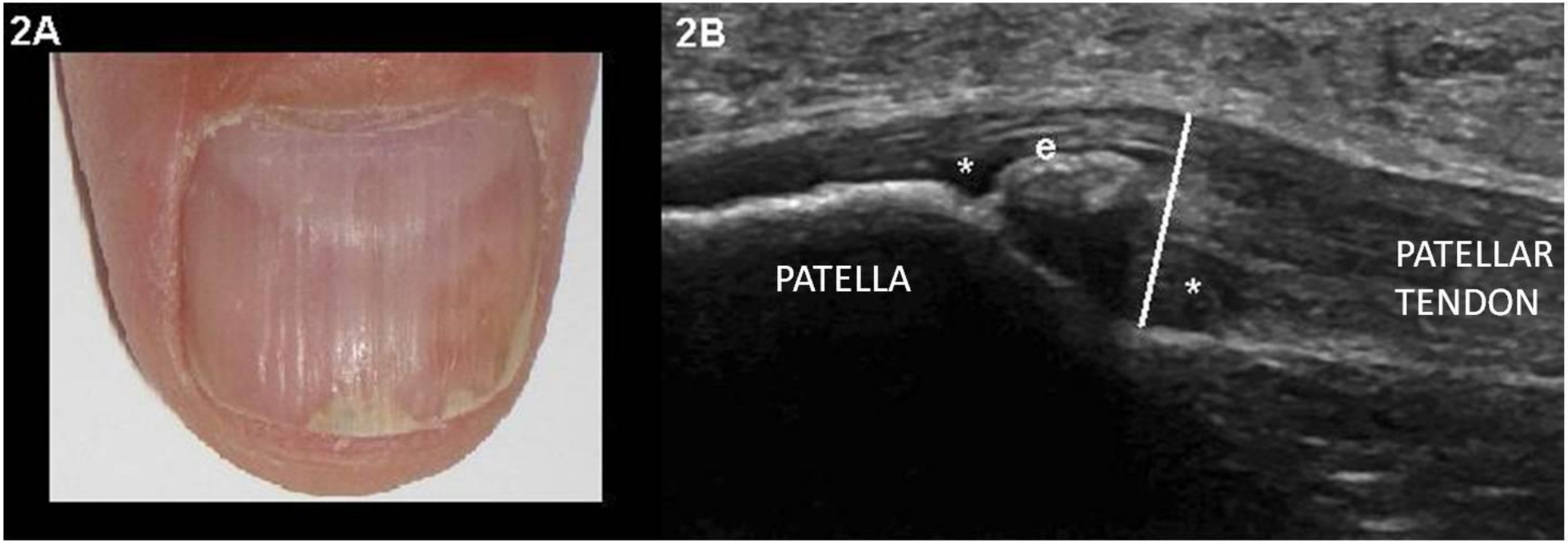


Table 12: Total number of US findings at all sites. PD refers to power Doppler.

	Psoriasis with nail disease (372 entheses)		**Psoriasis without nail disease (180 entheses)**		**p**
	n	**%**	**n**	**%**	
Hypoechogenicity	98	26	31	17	0.02
Thickening	146	39	41	23	0.0001
PD	3	1	2	1	0.7
Calcifications	18	5	5	3	0.4
Bursal enlargement	23	6	20	11	0.06
PD inside the bursa	1	0.3	2	1	0.3
Enthesophytes	152	41	57	32	0.04
Erosions	9	2	6	3	0.4

4.3.4 Bone erosion and spur formation

Patients with psoriasis had similar chronic changes to HC [8.5 (0-31) vs. 7 (1-24); p=0.08] (Figure 8). When patients with nail disease were compared separately, the nail disease group had considerably higher enthesopathy chronicity scores than HC [10 (0-31) vs. 7 (1-24); p=0.04]. Patients with nail disease had more enthesophytes than patients without nail disease (Table 12).

4.3.5 Total ultrasound scores

Patients with nail disease had higher total US scores [23 (0-65)] compared to patients without nail disease [15 (5-26); p=0.02] and HC [11 (3-39); p=0.005]. A detailed list of US findings depending on the site can be seen in Table 13.

Table 13: Frequency of US abnormalities at the different entheseal sites

		Psoriasis with nail disease (n=31 patients, 62 entheses)				**Psoriasis without nail disease (n=15 patients, 30 entheses)**			
		Enthesis		**Patient**		**Enthesis**		**Patient**	
		n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Achilles	Hypoechogenicity	9	15	7	23	0	0	0	0
	Thickening	12	19	8	26	0	0	0	0
	PD	0	0	0	0	0	0	0	0
	Calcifications	2	3	2	7	0	0	0	0
	Bursal enlargement	9	15	6	20	3	10	3	20
	PD inside the bursa	1	2	1	3	0	0	0	0
	Enthesophytes	51	82	28	90	24	80	13	87
	Erosions	1	2	1	3	0	0	0	0
Quadriceps	Hypoechogenicity	20	32	15	49	10	33	7	47
	Thickening	14	23	9	29	5	16	3	20
	PD	1	2	1	3	1	3	1	7
	Calcifications	3	5	2	7	2	7	2	13
	Bursal enlargement	3	5	3	10	2	7	2	13
	PD inside the bursa	0	0	0	0	0	0	0	0
	Enthesophytes	21	34	13	42	13	43	9	60
	Erosions	1	2	1	3	1	3	1	7

		Psoriasis with nail disease (n=31 patients, 62 entheses)				Psoriasis without nail disease (n=15 patients, 30 entheses)			
		Enthesis		Patient		Enthesis		Patient	
		n	%	n	%	n	%	n	%
Patellar origin	Hypoechogenicity	19	31	14	45	10	33	7	47
	Thickening	42	68	24	77	15	50	9	60
	PD	0	0	0	0	0	0	0	0
	Calcifications	3	5	3	10	0	0	0	0
	Bursal enlargement	1	2	1	3	0	0	0	0
	PD inside the bursa	0	0	0	0	0	0	0	0
	Enthesophytes	21	34	15	49	2	7	2	13
	Erosions	2	3	2	7	2	7	2	13
Patellar insertion	Hypoechogenicity	22	36	17	55	6	20	5	33
	Thickening	41	66	15	49	16	53	9	60
	PD	0	0	0	0	1	3	1	7
	Calcifications	3	5	3	10	3	10	2	13
	Bursal enlargement	9	15	7	23	15	50	8	53
	PD inside the bursa	0	0	0	0	2	7	1	7
	Enthesophytes	13	21	10	32	5	17	3	20
	Erosions	1	2	1	3	0	0	0	0

		Psoriasis with nail disease (n=31 patients, 62 entheses)				Psoriasis without nail disease (n=15 patients, 30 entheses)			
		Enthesis		Patient		Enthesis		Patient	
		n	%	n	%	n	%	n	%
Plantaris	Hypoechogenicity	9	15	8	26	3	10	3	20
	Thickening	15	24	11	36	2	7	1	7
	PD	0	0	0	0	0	0	0	0
	Calcifications	0	0	0	0	0	0	0	0
	Bursal enlargement	0	0	0	0	0	0	0	0
	PD inside the bursa	0	0	0	0	0	0	0	0
	Enthesophytes	24	39	17	55	4	13	3	20
	Erosions	4	7	3	10	2	7	2	13
CET	Hypoechogenicity	19	31	14	45	2	7	2	13
	Thickening	22	36	17	55	3	10	2	13
	PD	2	3	2	7	0	0	0	0
	Calcifications	7	11	6	19	0	0	0	0
	Bursal enlargement	1	2	1	3	0	0	0	0
	PD inside the bursa	0	0	0	0	0	0	0	0
	Enthesophytes	22	36	14	45	9	30	5	33
	Erosions	0	0	0	0	1	3	1	7

4.3.6 Link between clinical assessments and ultrasound findings

The link between the overall burden of nail disease extent and severity was explored using the mNAPSI scores in 36 patients. The severity of nail

disease correlated with the inflammation (r^2 =0.45, p=0.005) and chronicity scores (r^2 =0.35, p=0.04). The duration of psoriasis also tended to correlate with entheseal inflammation (r^2 =0.29; p=0.05) whereas no link between PASI and US scores was evident.

A further analysis was performed to exclude the effect of tenderness on physical examination and compared the US scores by excluding 4 patients with mild entheseal tenderness. The US scores showed the same statistical associations with nail disease (data not given).

4.4 Discussion

Given that nail disease is a predictor for PsA evolution and that the nail is functionally integrated with a network of entheses about the distal interphalangeal joints, the hypothesis tested was that nail involvement in psoriasis was linked to a more extensive subclinical enthesopathy. These findings confirm that subclinical enthesopathy was common and was specifically related to nail disease. It was also found that more extensive nail involvement correlated with more severe enthesopathy scores. Subgroup analysis to look at different patterns of nail disease would be interesting but was not possible due to the co-existence of different patterns within the same patient, and the small numbers that would be involved.

What is the pathophysiological basis for these findings? It has recently been shown that nail disease in psoriasis most typically affects the dominant hand thumb nail and then other nails that are most associated with hand function (Rich et al. 2008). This points towards tissue specific factors rather than autoimmunity in general as being key drivers in the psoriatic onychopathy process. Given that Koebnerisation responses in the skin occur in the presence of tissue trauma or an aberrant repair response to it, then it is possible that much of the nail disease process is linked to joint mechanics and / or trauma (Buckley et al. 1959; McGonagle et al. 1999). The genetic basis for these changes awaits elucidation.

There is also a clear epidemiological link between PsA and joint trauma and, perhaps of even greater relevance, is the observation that normal entheses have evidence for microscopic damage and associated inflammatory changes that likely represent part of the normal healing process (Punzi et al. 1998; Benjamin et al. 2007b; Pattison et al. 2008). Therefore, the subclinical enthesopathy noted in psoriasis cases with nail disease may point towards an aberrant response to tissue micro-damage at diverse sites. However, it may be that the genetic factors that predispose to nail disease may also help switch subclinical enthesopathy into a manifesting inflammatory enthesitis. At this point, it must be accepted that the actual basis for the link between nail disease and distant enthesopathy awaits elucidation and that other putative mechanisms may exist.

In conclusion this study confirms that enthesopathy is common in psoriasis patients without clinical arthritis. Moreover subclinical enthesopathy is especially associated with nail involvement in a cross sectional analysis. These findings suggest that nail disease is in some way linked to the expression of enthesitis including subclinical disease.

Chapter 5
Comparison of the ultrasound appearances of peripheral enthesitis in psoriasis and psoriatic arthritis patients and healthy controls

5.1 Introduction

During the last decade it has emerged that enthesitis and associated osteitis are the common denominators underlying the multifaceted skeletal manifestations of psoriatic arthritis (PsA) that include axial and appendicular disease (McGonagle et al. 1999). In keeping with the importance of enthesitis as the key pathologic lesion in PsA, some studies have shown enthesopathy in asymptomatic large insertions of the lower limbs in patients with spondyloarthropathies including PsA (Balint et al. 2002). This is reminiscent of studies in inflammatory oligoarthritis where ultrasound detected synovitis in joints which were clinically uninvolved (Wakefield et al. 2004). Of even greater importance is that several studies have shown subclinical enthesopathy or osteitis in up to 50% of psoriasis patients with no musculoskeletal symptoms (McGonagle et al. 2011a).

As detailed in chapter two, ultrasonography (US) is well suited to the assessment of entheses. In recent years, power Doppler (PD) US has been increasingly used in rheumatology as it identifies vascular abnormalities known to be associated with inflammation. PD US to some extent provides a reflection of the degree of angiogenesis, which is critically related to joint damage and therapeutic responses to drugs (Naredo et al. 2008; Aydin et al. 2010b; Kurosaka et al. 2010; Hammer et al. 2011). Extra-articular PD signal has been demonstrated in both PsA and psoriasis patients (Fournié et al. 2006; Gutierrez et al. 2011a; Gutierrez et al. 2011b; Ash et al. 2012b). However, there is limited work directly comparing PD changes at the insertions between patients with PsA and psoriasis.

The purpose of this study was to undertake US of symptomatic and asymptomatic insertions in cases with PsA and cases with psoriasis, the

latter having no clinical arthritis. The hypothesis tested was that the imaging phenotypes might differ between PsA patients and psoriasis cases without clinical arthritis. Specifically, it was hypothesised that the enthesopathy associated with PsA would have a greater degree of vascularisation compared to that seen in psoriasis without arthritis. It was also postulated that subclinical vascular changes at the entheses might be associated with more widespread disease activity in PsA. Such an imaging biomarker could be helpful in understanding and predicting the disease evolution from psoriasis to PsA, which at the present time is not fully understood.

5.2 Methods

The study was carried out at two European centres - at the Leeds Teaching Hospitals (UK) and the University Hospital Department of Verona (Italy). Ethical approval for the study was obtained at both sites.

5.2.1 Patient groups and clinical assessment

One hundred consecutive patients (42 with psoriasis and 58 with PsA) and 23 healthy controls (HC) were recruited. Seventy-four patients were recruited in the UK, 26 patients and the healthy controls were recruited in Italy. PsA patients were included if they fulfilled the CASPAR criteria (Taylor et al. 2006). Psoriasis patients were excluded if they had a current or previous history of arthralgia, arthritis or enthesitis. The clinical assessment was performed by one rheumatologist at each centre, who was blinded to the US data. This assessment included the psoriasis area and severity index (PASI), tender and swollen joint counts (TJC, SJC), a dactylitis count and the Leeds and SPARCC enthesitis indices in the patients with PsA. Patients receiving glucocorticoids and anti-TNF therapies were excluded from the study, those receiving DMARD therapy were recruited if they had active skin or joint disease (inadequate responders).

5.2.2 Ultrasonography

Ultrasound scanning of the peripheral entheses was performed as described in chapter four although the common extensor origin was excluded for this study.

5.2.2.1 Ultrasound image interpretation

Ultrasound images were scored according to the system described in chapter four. It is now recognised that the enthesis represents an integrated organ comprising the insertion (which is avascular in health) and adjacent tendon, fibrocartilages and the immediately adjacent synovium where present (Benjamin et al. 2009). For the PD assessment the sonographers therefore looked for PD signal in all the components of the enthesis organ, including signals at the insertion and inside the adjacent bursa, wherever these were present. It is not possible to define the margins of the enthesis by US, however the entheseal vascularity was assessed when the Doppler signal was close to the cortical bone.

5.2.3 Statistics

Data are expressed either as frequencies, means (standard deviation) or medians (range) according to the variability. The prevalence of each individual lesion by US in patients with or without arthritis was compared by using a chi-square test. The Mann-Whitney U test was used to compare US scores between groups.

Correlations between clinical parameters (TJC, SJC, PASI, and disease duration) and US scores (separately for US scores related to inflammation, damage and total) were analysed using the Pearson correlation test. Statistical analysis was performed using SPSS version 11.5.

To provide agreement between sonographers, all investigators agreed on definitions and the scoring system prior to the study both on saved images and while acquiring sample images. Stored images from the first 21 patients included in the study (total 1020 images) were scored by all three sonographers for grey scale and PD for all entheses. ICC values were

calculated for each pair of investigators and for all type of US scores used in the purpose of this study.

5.3 Results

5.3.1 Inter-observer agreement on sonography scoring

A moderate to excellent agreement between both investigator pairs was found for different scores: for GS inflammation the ICC values were in the range 0.91-0.93 (95% CI: 0.79-0.97), for PD inflammation 0.74-0.95 (95% CI: 0.45-0.98), for chronicity scores 0.89-0.93 (95% CI: 0.76-0.98) and for total US scores 0.92-0.95 (95% CI: 0.81-0.98).

5.3.2 Patient characteristics

Patients and HCs were of similar age [46.3 (15) vs. 52.2 (11) respectively; p=NS] and body mass index [26.7 (19.3-42.4) vs 24.2 (21-31.3); p=0.08]. The gender distribution was also similar in both groups (43% female in the psoriasis group and 52% in the HC). None of the patients with psoriasis had clinical enthesitis compared to 51.7 % of the patients with PsA (30/58). In the PsA patients, the median tender joint count was 4 (0-20) and the swollen joint count was 4 (0-19). PASI scores were slightly lower in the patients with PsA [3.3 (0-18)] compared to those with psoriasis [4.3 (0-22); p=0.02)]. The groups had similar disease durations [19.1 (12.5) years for PsA and 17.5 (11) years for psoriasis]. In general, hypoechogenicity, thickening and enthesophytes were the most frequent US findings for each site, whereas PD and erosions were relatively rare (Table 14) (Figure 10). These findings are described in more detail below.

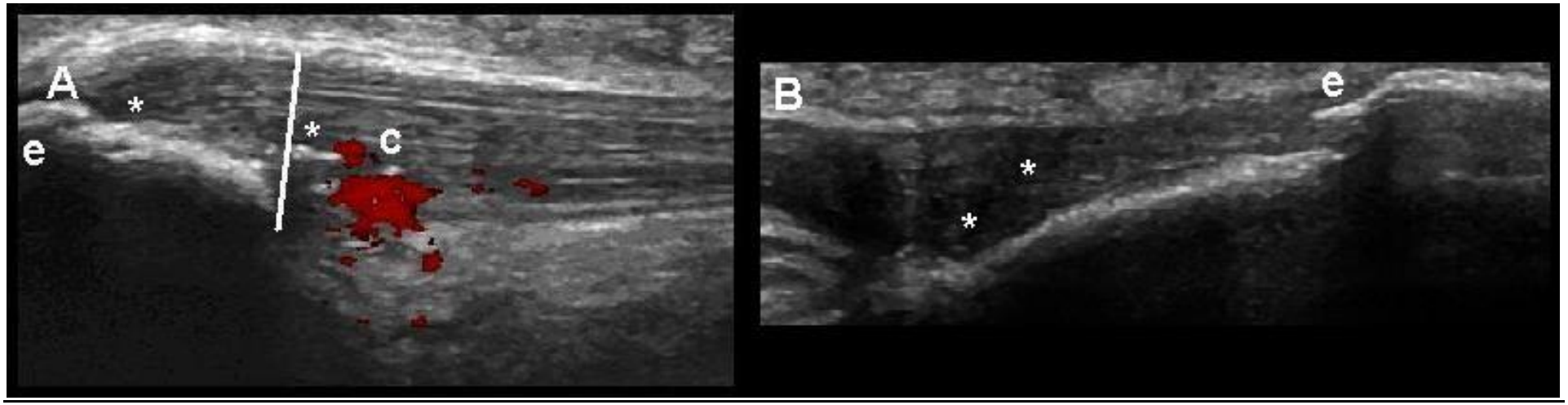
Table 14: Total number of US findings at all sites

	Healthy controls (230 entheses)	**Psoriasis (420 entheses)**	**PsA (580 entheses)**	**p value (*)**
	n (%)	**n (%)**	**n (%)**	
Hypoechogenicity	29 (12.6)	105 (25)	208 (35.9)	0.0003
Thickening	69 (30)	162 (38.6)	250 (43.1)	0. 15
PD	0 (0)	2 (0.4)	12 (2.1)	0.05
Calcifications	22 (9.6)	17 (4.1)	57 (9.8)	0.0005
Bursal enlargement	3 (1.3)	35 (8.3)	77 (13.3)	0.02
PD inside the bursa	0 (0)	3 (0.7)	16 (2.8)	0.02
Enthesophytes	90 (39.1)	180 (42.9)	297 (51.2)	0.01
Erosions	1 (0.4)	12 (2.9)	29 (5)	0.1

*: p values are given for comparisons between groups with PsA and psoriasis

Figure 10. Ultrasound appearances of enthesitis

Examples of ultrasound findings of enthesitis in psoriatic arthritis (A) and psoriasis (B). A: The origin of the patellar tendon with moderate thickening (white line), hypoechogenicity (*), a small enthesophytes (e), calcifications (c) and power Doppler signals inside the enthesis. B: The insertion of the patellar tendon with moderate hypoechogenicity (*) and a large enthesophytes (e).



5.3.3 Soft tissue changes at insertions

As expected, patients with psoriasis (with or without arthritis) had higher enthesitis scores related to inflammation than HC (for inflammation $p<0.0001$, for total US scores $p<0.0001$). The PsA patients had higher US scores than both psoriasis patients without arthritis (for inflammation $p=0.04$, for total US scores $p=0.02$) and HC (for inflammation $p<0.0001$, for total US scores $p<0.0001$) (Table 14). Certain findings including hypoechogenicity and bursal enlargement were more frequent in PsA compared to psoriasis (Table 14).

5.3.4 Power Doppler evaluation

Doppler positivity in at least one entheseal site was observed more frequently in PsA (21/58, 36.2 %) than in psoriasis (4/42, 9.5%; $p=0.002$). Doppler signal was not seen in any healthy controls. The presence of Doppler positivity had a sensitivity of 36% (95%CI: 24-50%) and a specificity of 91% (95%CI: 77-97%) with a positive likelihood ratio of 3.8 to discriminate PsA and psoriasis. The most discriminative site for PD positivity was the retrocalcaneal bursa (seven PsA vs. one psoriasis patient). Furthermore, six patients had PD signal at more than one site and 5 of these patients had PsA.

5.3.5 Bone erosion and spur formation

Psoriasis patients (with or without arthritis) had more chronic changes compared with HC ($p=0.02$). The PsA patients had higher chronicity scores than both patients with psoriasis ($p=0.02$) and HC ($p=0.003$) (Table 14). This may reflect previous episodes of inflammation. Calcification and enthesophytes were also more frequent in the entheses of patients with PsA compared to the psoriasis group, which may be in keeping with previous inflammatory episodes with subsequent tissue remodelling (Table 14).

Table 15: Median entheseal US scores for healthy controls, PsA and psoriasis patients.

		Healthy controls (n=23)	**Psoriasis (n=42)**	**PsA (n=58)**	**PsA (symptomatic enthesitis excluded) (n=28)**
Ultrasound findings related to inflammation	**GS score**	4 (0 – 15)	9.5 (0 – 30)	11.5 (1 – 44)	12 (2 – 44)
	PD score	0 (0 – 0)	0 (0 – 3)	0 (0 – 7)	0 (0 – 4)
	Total inflammation score	4 (0 – 15)	9.5 (0 – 30)	13 (1 – 46)	12.5 (2 – 46)
Chronicity score		6 (1 – 22)	8 (0 – 25)	10 (2 – 29)	10 (2 – 24)
Total ultrasound score		10 (3 – 36)	16 (0 – 55)	21.5 (4 – 69)	23 (4 – 69)

GS: grey scale, HC: healthy control, PD: power Doppler, PsA: psoriatic arthritis

Numbers are given as median (range)

5.3.6 Clinical assessments and their association with ultrasound findings

When patients with clinical enthesitis were excluded from the PsA group, patients with arthritis still had higher PD enthesopathy scores than patients with psoriasis (p=0.003), as well as higher chronicity scores (p=0.01) (Table 15). The tender joint counts (TJC) (r^2 =0.21; p=0.03) and swollen joint counts (SJCs) (r^2 =0.29; p=0.003) correlated to entheseal Doppler scores. Furthermore, the SJC correlated to total US scores (r^2 =0.21; p=0.03). No link between PASI and disease duration and US scores was evident.

5.4 Discussion

This study showed that the frequency of enthesis-related PD change was significantly higher in PsA compared to psoriasis even when only sites of asymptomatic enthesopathy were evaluated in PsA. Moreover, the frequency of subclinical enthesopathy was significantly higher in PsA compared to psoriasis. The results of this cross-sectional study suggest that there may be a trend towards increased entheseal thickening with subsequent vascular changes representing a step in the progression towards PsA in psoriasis cases. This will require confirmation in a longitudinal study.

It is noteworthy that abnormal patterns of vascularity have been reported in psoriatic arthritis synovium both by arthroscopic inspection and by histological assessment (Reece et al. 1999; Fearon et al. 2003). Likewise prominent vascular changes have been reported in skin disease and at the nail matrix in psoriasis (Zaric et al. 1982; Creamer et al. 1997). Furthermore, normal entheseal insertions are sites prone to microdamage and in the course of physiological tissue repair at such sites prominent histological evidence for vascular changes is seen even in healthy subjects (Benjamin et al. 2007b). This study found a high prevalence of enthesophytes in the healthy controls. Enthesophytes are not specific to

enthesitis and may be related to mechanical forces. This finding also reflects the high sensitivity of US to detect these changes.

In this study, no entheseal PD signals were seen in the HC group. The majority of the literature supports the absence of US detectable blood flow in normal subjects (Naredo et al. 2011), PD changes have been reported in a few cases (de Miguel et al. 2011b). This raises the possibility of using Doppler signals for early diagnosis, although this would need to be demonstrated in prospective trials.

This study was performed in two different European populations by different sonographers, which raises issues about its reliability and general applicability. However, both study populations exhibited identical trends in patterns of disease. Likewise the sonographers met and agreed on standard sonographic criteria for enthesitis and the inter-observer agreement was quite high.

Taken together these findings now need to be applied in a large inception cohort of psoriasis patients to ascertain whether they define the subgroup that will be likely to evolve into PsA in the following months and years. In that regard, US has previously been used to show a high frequency of subclinical entheseal involvement in patients presenting with psoriasis but without clinically evident arthritis (Gisondi et al. 2008). After following this cohort for 3.5 years a link was demonstrated between subclinical enthesopathy in patients with psoriasis and the future development of PsA (Tinazzi et al. 2011).

In conclusion, this study shows that the degree of systemic subclinical enthesopathy is much greater in PsA compared to psoriasis. Of particular note the difference in vascular changes in PsA compared to psoriasis might have implications for determining the likelihood of a given patient progressing to PsA. This will form the basis for future studies.

Chapter 6
High resolution magnetic resonance imaging of the distal interphalangeal joint and nail in psoriasis and psoriatic arthritis

6.1 Introduction

Although PsA was historically considered in relationship to synovial inflammation it has emerged that enthesitis and associated osteitis are the common denominator at the different sites of skeletal inflammation (McGonagle et al. 1998a; McGonagle et al. 1999). In keeping with the importance of enthesopathy in PsA, imaging studies in patients with psoriasis without clinical arthritis have also shown a high prevalence of subclinical entheseal changes in peripheral large joint entheses such as the Achilles tendon (Namey et al. 1976; Offidani et al. 1998; Ozcakar et al. 2005; Erdem et al. 2008; Gisondi et al. 2008; Raza et al. 2008; Emad et al. 2010).

Of particular clinical relevance to both rheumatologists and dermatologists is that nail disease is more strongly associated with PsA than psoriasis and its presence in the latter is a predictive factor for the later development of PsA (Wilson et al. 2009a). Enthesitis in DIP joint disease in PsA is common on high resolution MRI in clinically active joints (Tan et al. 2006a). Furthermore, the nail is anchored directly to the skeleton via a network of entheses around the DIP joint (Tan et al. 2007). As shown in chapter four, the presence of nail disease in psoriasis is also associated with a greater degree of subclinical enthesopathy at distant sites in the lower limbs (Ash et al. 2012b).

Given the intimate link between the nail and the entheses, this study explored the extent of enthesopathy present in psoriasis related nail disease and the degree of underlying associated bone changes. To address this, a

spectrum of PsA and psoriasis cases with and without nail involvement were compared to assess the underlying DIP joint and surrounding soft tissues using MRI.

6.2 Methods

Ethical approval was gained from the local ethics committee and all patients gave written consent. Cases were recruited consecutively from the dermatology and rheumatology clinics of the Leeds and Harrogate teaching hospitals between March 2011 and November 2012. Psoriasis cases were recruited based on a diagnosis of psoriasis confirmed by a dermatologist, but were only recruited if they had no current arthralgia or arthritis or history suggestive of PsA. The PsA cases all fulfilled the CASPAR criteria (Taylor et al. 2006). Patients receiving biological therapies were excluded, but those on systemic immunosuppression were included if they had persistent active disease.

All patients underwent a clinical assessment including Psoriasis Area and Severity Index (PASI), Body Surface Area affected with psoriasis (BSA), modified Nail Psoriasis Severity Index (mNAPSI) (Cassell et al. 2007), a 76 tender and swollen joint count, an assessment for clinical enthesitis (Leeds Enthesitis Index [LEI] (Healy et al. 2008b) and Spondyloarthritis Research Consortium of Canada enthesitis index [SPARCC]) (Maksymowych et al. 2009) and a dactylitis count. Patients also reported any painful or tender nails and completed visual analogue scales for global, psoriasis and arthritis disease activity as well as nail pain. Quality of life was assessed using the Dermatology Life Quality Index (DLQI) (Finlay et al. 1994) and psoriasis patients also completed the Psoriasis Epidemiology Screening Tool (PEST) (Ibrahim et al. 2009).

A high resolution MRI was performed of one finger using a 3-T Verio scanner (Siemens Healthcare, Erlangen, Germany). The finger to be scanned was selected on the basis of the most severely affected nail. In patients with normal nails, the index or middle finger was chosen. The scan included intermediate-weighted sagittal, fat-suppressed proton density axial,

T2 coronal and T1 post contrast sequences. A 4cm loop coil was used to image from the finger-tip to the middle phalanx. Gadolinium contrast was given unless contra-indicated, and petroleum jelly was applied to the nail to delineate the outer contour, as described by Scarpa et al. (Scarpa et al. 2006b).

The MRIs were scored by two experienced musculoskeletal radiologists by consensus. The radiologists were blinded to the diagnosis. The scoring system used has previously been reported (Tan et al. 2006a). It included anatomical structures (cartilage, collateral ligaments, flexor and extensor tendons), synovitis post-contrast and bone marrow lesions (BMLs) on proton density / T2 weighted fat suppressed spin echo images. Anatomical structures were recorded dichotomously as normal or abnormal. Synovitis and effusion were graded 0-2 on a semi-quantitative basis and BMLs were graded from 0-3. Features of enthesopathy scored included tendon tears, tendon thickening, signal change within the tendon, peri-ligamentous high signal, BMLs or erosions at the enthesis.

6.2.1 Statistical analysis

Categorical data are expressed as frequencies (percentages). Fisher's exact 2-tailed test was used to compare the proportions of patients with certain findings between groups, with differences considered significant if the P value was less than 0.05.

6.3 Results

6.3.1 Demographic data

A total of 57 patients were recruited; 29 patients with PsA and 28 patients with psoriasis without arthritis or arthralgia. The mean patient age was 41 (range 18 – 83), 47% of the patients were female.

6.3.2 Clinical data

When assessed at baseline, 14 of the PsA patients had clinical nail disease, while 15 had normal nails. Seven out of 29 (24%) of the PsA patients had clinically active arthritis (tenderness or swelling) in the DIP joint scanned at the time of the assessment. Of the remaining 22, 3 had current tenderness or swelling in another DIP joint (but not the one scanned) and a further four had previously had DIP disease but had no current DIP activity. For the PsA patients, the mean swollen joint count was 5, tender joint count 7, LEI 1 and SPARCC 3. Only one patient had dactylitis in the digit that was scanned.

Among the psoriasis patients, 17 had nail disease and 11 psoriasis patients had normal nails. The mean PASI was 3.0 in the PsA patients and 5.9 for psoriasis. Fifty-two percent of the PsA patients were on disease modifying therapies. Of the psoriasis patients, 11% were not receiving any treatment, 25% were using topical treatments only, 25% were having phototherapy and 39% were on systemic immunosuppression (ciclosporin or methotrexate).

6.3.3 Magnetic resonance imaging results

In keeping with previous data, the PsA cases with active DIP arthritis had diffuse inflammation around the DIP joint including BMLs 4/7 (57%), nail bed changes, extensor or flexor tendon enthesopathy 4/7 (57%) and synovitis 5/7 (71%). Subclinical enthesopathy and BMLs were seen even in asymptomatic (non-tender and non-swollen) DIP joints in the PsA patients (BMLs in 6/22 (27%), extensor or flexor tendon enthesopathy in 5/22 (23%), synovitis in 6/22 (27%)). As further described below, a proportion of patients with psoriasis but no clinical PsA had evidence for enthesopathy, synovitis and BMLs (Table 16). The severity of the changes seen was markedly higher in the PsA patients than the psoriasis patients.

Table 16. Frequency of different findings in PsA and psoriasis patients

	Psoriatic arthritis				**Psoriasis**	
	Active DIP arthritis n=7	**Clinically inactive DIP joint n=22**			**Nail disease n=17**	**Normal nails n=11**
		Overall n=22	**Nail disease n=11**	**Normal nails n=11**		
Bone marrow lesions	57%	27%	45%	9%	12%	9%
Synovitis	71%	27%	27%	27%	19%	30%
Extensor tendon enthesopathy	57%	14%	27%	0%	0%	0%
Flexor tendon enthesopathy	14%	14%	27%	0%	6%	0%

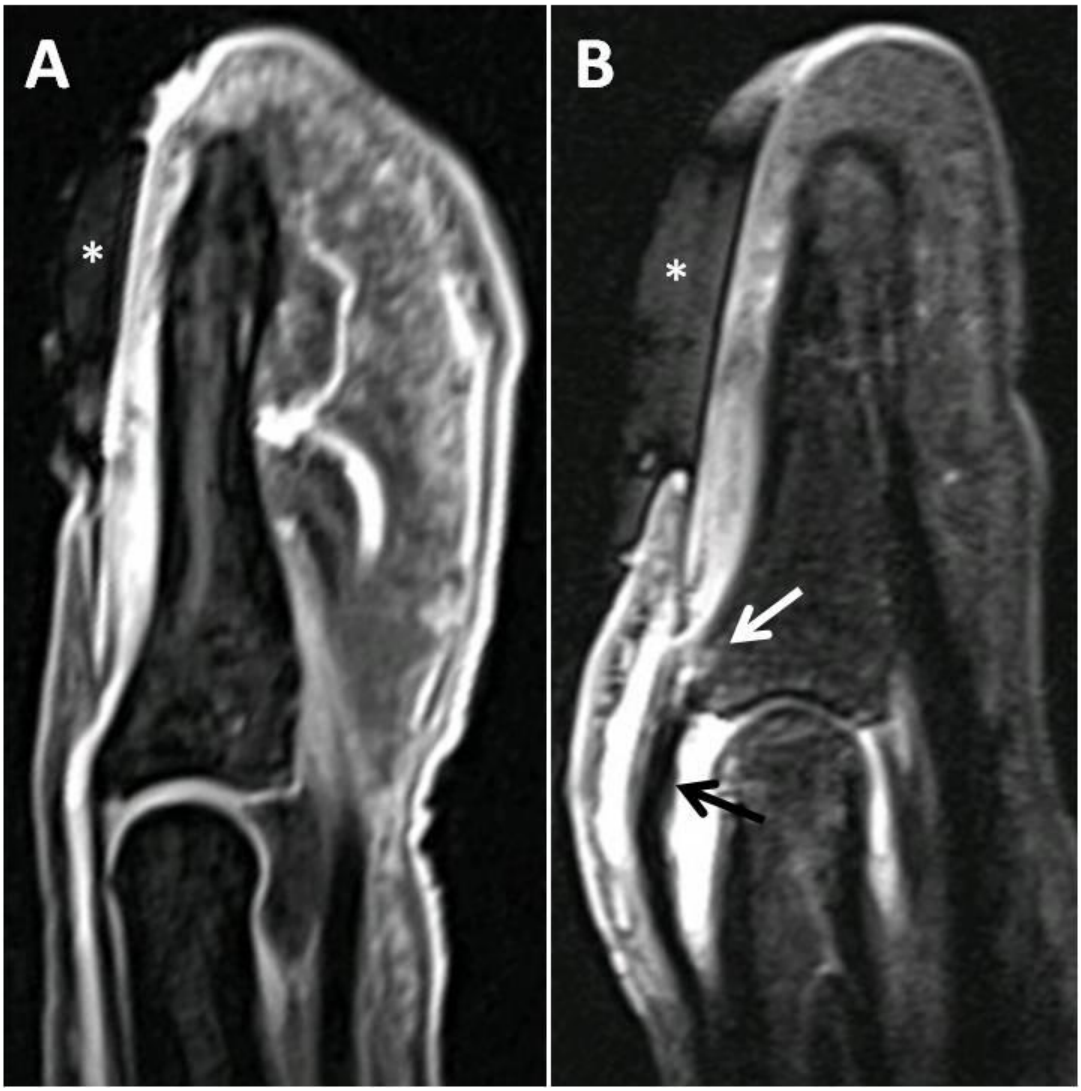
6.3.4 Extensor tendon enthesopathy

Extensor tendon (ET) enthesopathy (as measured by tendon thickening, signal change and BMLs) was seen only in PsA patients and not in psoriasis patients (7/29 (24%) vs. 0/28 (0%), p=0.01). Within the PsA patients, ET enthesopathy was seen more frequently in the presence of nail disease (5/14 (36%) in patients with nail disease vs. 2/15 (13%) in patients with normal nails, p=NS) (Figure 11). Given the potential link between these tendon changes and adjacent nail disease, the frequency of different types of nail changes was assessed. In PsA patients with nail disease, pitting was seen in 4/5 (80%) of those with extensor tendon enthesopathy and 6/9 (67%) of those with normal extensor tendons. Onycholysis was seen in 5/5

(100%) of those with extensor tendon enthesopathy and 6/9 (67%) of those with normal extensor tendons.

Figure 11. Examples of normal and abnormal extensor tendons

The petroleum jelly appears overlying the nail (asterisk). A: normal extensor tendon. B: thickened extensor tendon in a PsA patient (black arrow) with osteitis and high signal (white arrow) at the insertion.



6.3.5 Flexor tendon enthesopathy

High signal at the insertion of the DIP flexor tendon (FT) was seen only in patients with clinical nail disease (4/14 (29%) in PsA patients with nail disease and 1/17 (6%) in psoriasis patients with nail disease). This difference was statistically significant between PsA patients with and without nail disease (p=0.04). No flexor tendon disease was seen in patients with normal nails irrespective of the presence of psoriasis or PsA.

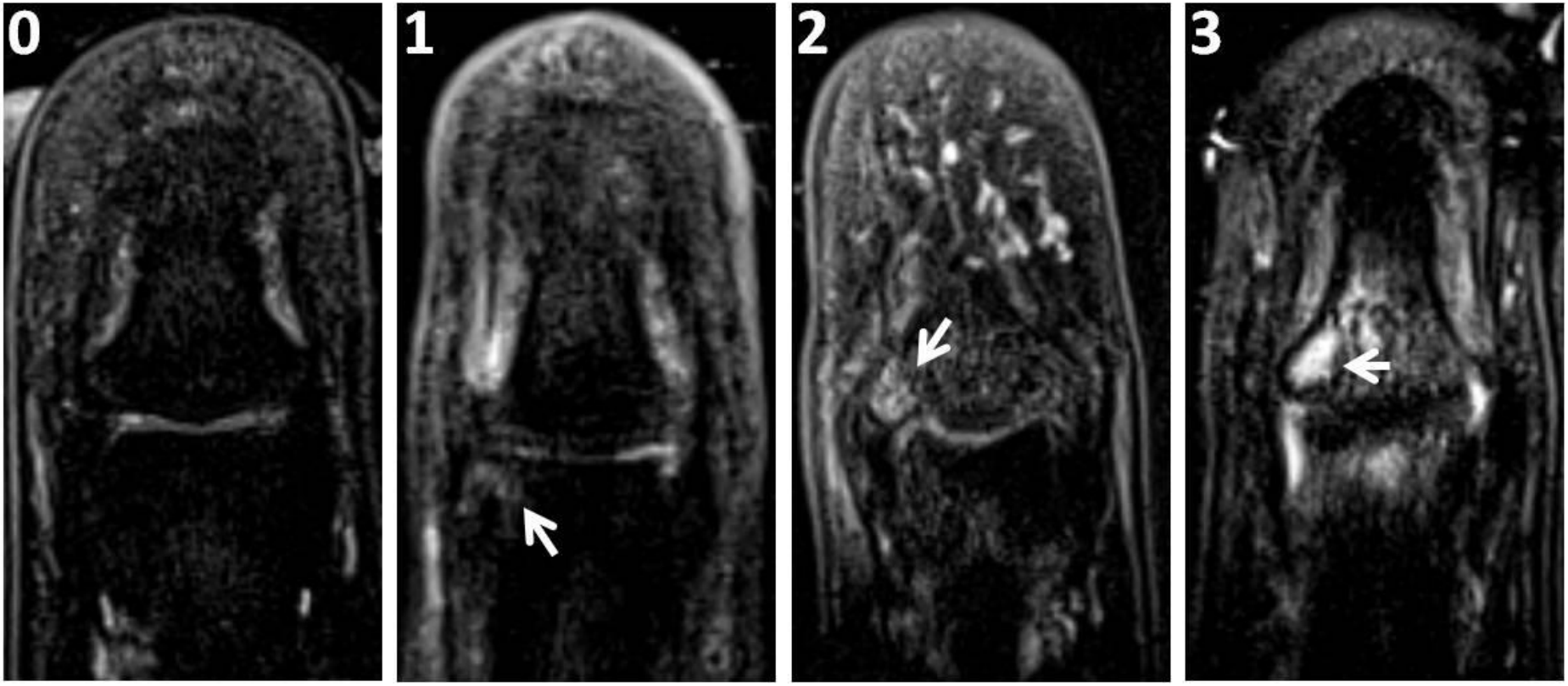
6.3.6 Magnetic resonance imaging-determined bone marrow lesions

The prevalence of BMLs of the DIP joint was much greater in PsA compared to psoriasis. BMLs were seen in (4/7) 57% in PsA patients with active DIP arthritis compared to 6/22 (27%) in PsA patients with a clinically inactive DIP joint p=NS). In contrast, 2/17 (12%) of psoriasis patients with nail disease and 1/11 (9%) of psoriasis with normal nails were noted to have BMLs.

Moreover, the severity and extent of BMLs varied greatly between PsA and psoriasis, with no psoriasis patient demonstrating a BML score of greater than grade one (mild) (Figure 12). Within the PsA patients, in those DIP joints that were clinically active (tender or swollen, n=7) 3/7 (43%) had no BMLs and 4/7 (57%) had grade 2-3 BMLs. In PsA patients with clinically inactive DIP joints, 16/22 (73%) had no BMLs, 5/22 (23%) had grade one and 1/22 (5%) had grade three BMLs.

Figure 12. Examples of BMLs

Examples of BMLs (white arrows) grade 0, 1, 2 and 3 (scored as the maximum intensity seen within each patient not overall extent)



6.3.7 Synovitis

In PsA patients with a clinically active DIP joint, MRI synovitis was seen in 5/7 (71%) patients, in PsA patients with a clinically inactive joint, subclinical synovitis was seen in 6/22 (27%). In psoriasis patients, subclinical Gd-DTPA enhancement suggestive of synovitis was seen in 3/16 (19%) of those with nail disease and 3/10 (30%) of those with normal nails.

6.3.8 Nail bed and nail matrix lesions

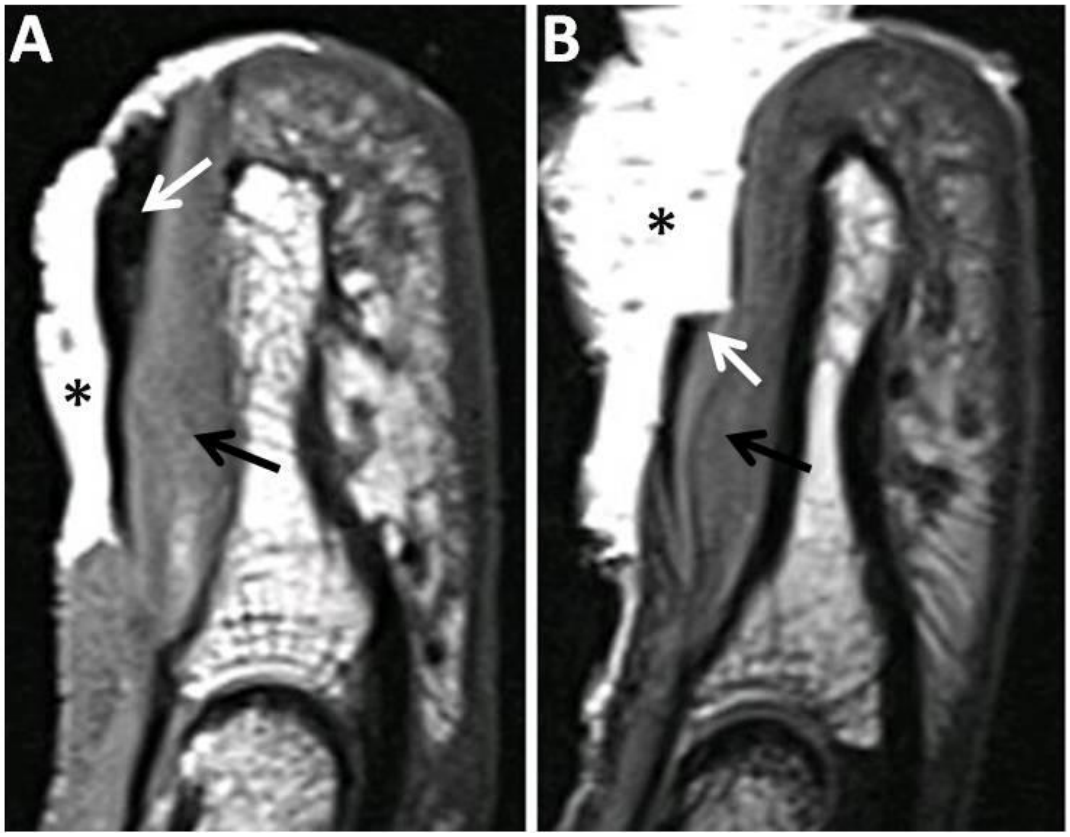
The majority of patients with nail disease had features of both nail bed and nail matrix lesions. Of all nails scanned, eight had only features of nail bed psoriasis and six had only features of nail matrix psoriasis. There were no substantive differences in the prevalence of different clinical nail features between the PsA and psoriasis patients. Due to the small numbers no analysis was performed to assess differences in underlying soft tissue or bony changes between the groups.

6.3.9 Imaging of the nail

Abnormalities of the nail itself were apparent by MRI in 12/31 (39%) of the patients with nail disease, with a specificity of 100%. These tended to be the patients with more severe nail disease (median mNAPSI 24 in those with MRI-evident nail disease vs. 16 in those with clinical nail disease that was not visible on MRI). Thickening of the nail bed was also seen in some patients with nail disease (Figure 13).

Figure 13. MRI appearances of psoriatic nail disease

A: MRI of a patient with psoriasis with clinical nail disease showing thickening and irregularity of the nail plate (white arrow) and nail bed (black arrow). B: MRI of a patient with PsA and nail disease demonstrating nail plate crumbling with loss of half of the nail (white arrow) and thickening of the nail bed (black arrow). The petroleum jelly appears bright (asterisk).



6.3.10 Collateral ligament enthesopathy

Collateral ligament enthesopathy was seen in 15/29 (52%) PsA patients and 12/28 (43%) psoriasis patients. Collateral ligament enthesopathy was more common in subjects over 40 years old (61% vs. 31%, p=0.03), in keeping with previous reports describing age related changes in healthy subjects (Tan et al. 2005). Collateral ligament changes therefore seem to be more likely to relate to normal age-related changes than psoriatic pathology.

6.4 Discussion

The purpose of this study was to use MRI to explore the link between enthesopathy and bone changes with nail disease in PsA and psoriasis. Although the magnitude of skeletal changes were substantially less than in PsA patients, there was nevertheless evidence for subtle subclinical inflammation around the DIP joint in a subgroup of psoriasis patients. This is in keeping with published data finding enthesopathy in a significant proportion of psoriasis patients in sites such as the knee, Achilles tendon and other large joint areas (Namey et al. 1976; Offidani et al. 1998; Ozcakar et al. 2005; Erdem et al. 2008; Gisondi et al. 2008; Raza et al. 2008; Emad et al. 2010). Subclinical enthesopathy may have implications for the development of PsA in psoriasis patients, with one study finding a higher rate of PsA development after three years in psoriasis patients with more subclinical enthesopathy at baseline (Tinazzi et al. 2011).

A clear link was shown between MRI determined extensor tendon enthesopathy in PsA and nail disease in PsA. Contrary to the hypothesis, these data do not show a relationship between the presence of inflammation at sites around the DIP joint and nail disease in psoriasis patients. These findings may reflect the relative lack of sensitivity of MRI to detect the more subtle enthesis changes seen in psoriasis subjects.

An unexpected finding in this study was the association of flexor tendon enthesopathy with nail involvement in PsA. It is noteworthy that on full flexion of the DIP joint in gripping or climbing actions, considerable forces are likely to be transmitted to the nail. Moreover, fibrous tissue from the flexor tendon merges with fibres from the extensor tendon, forming a lateral lamina which attached to the nail root and matrix and likely provides anchorage to the lateral aspects of the nail bed, but this has not been studied in great detail (Tan et al. 2007). These findings support emerging data from a positron emission tomography (PET) study showing that the nails and bone form a functionally integrated network (Tan et al. 2013).

The findings of this study are limited by the relatively low numbers in each patient group, which prevent analysis of further subgroups. No control group is available for comparison, however given the very low prevalence of

abnormalities in the psoriasis group, this would be unlikely to add much. A number of the patients were receiving systemic treatments for their skin or joint disease, and given that these may treat enthesopathy or arthritis this may have affected the findings. This was a pragmatic cohort recruited on the basis of active skin or joint disease and thus you would not expect the enthesopathy to be fully controlled. This was a pilot study and the imaging scoring used is not a validated system, although it has been used previously to study the DIP joint. The PsAMRIS scoring system for PsA affecting the hands was not designed to score ligaments and entheses so was not suitable for use in this study (Boyesen et al. 2011). Finally, whilst the radiologists were blinded, in some severe cases the arthritis or nail disease was very easily apparent on MRI.

In conclusion, this the first MRI study to assess the underlying DIP joint musculoskeletal changes in psoriasis patients with and without nail disease. Some psoriasis patients had subtle subclinical enthesopathy in the same sites as is seen in PsA-related nail disease. However the magnitude of the associated bone changes, where present, was much less. Flexor tendon entheseal changes were evident in some cases, which are likely to be relevant as the nails, bones and tendons are functionally integrated.

Chapter 7
Ultrasound imaging of the nail and distal interphalangeal joint and nail in psoriasis and psoriatic arthritis

7.1 Introduction

The importance of nail disease in subjects with psoriasis is being increasingly recognised (Baran 2010). Clinically, nail disease is associated with pain, functional loss, disfigurement and psychological distress (de Jong et al. 1996). From the rheumatological perspective, the presence of nail disease is a predictor for the development of PsA (Wilson et al. 2009a). In PsA patients, nail disease is associated with arthritis of the DIP joint (Jones et al. 1994; Williamson et al. 2004a). The nail is directly anchored to the underlying bone by structures including the extensor tendon (Tan et al. 2006b; Tan et al. 2007; McGonagle et al. 2009a). Enthesopathy is a generalised feature of both psoriasis and PsA. As shown in chapter four, in psoriasis patients nail disease is associated with a greater degree of systemic enthesopathy (Ash et al. 2012b).

Presently, assessment of nail disease is difficult given the limited utility of clinical assessment tools for the nail, which include the nail psoriasis severity index (NAPSI) and the modified NAPSI (mNAPSI) (Rich et al. 2003; Cassell et al. 2007). Recently magnetic resonance imaging, ultrasonography (US) and optical coherence tomography have been reported as possible tools for a more objective assessment of nail disease (Mogensen et al. 2007; Gutierrez et al. 2009; Soscia et al. 2009; Aydin et al. 2011). US has wide availability in the rheumatology setting, modest costs, a high resolution and allows good visualisation of tendons and entheses. With respect to the nail matrix region, this study aimed to determine whether US had the capability to detect local DIP joint enthesopathy in PsA and psoriasis patients. No US based imaging study of the nail has considered the matrix region before. Therefore this study assessed the utility of US for the assessment of psoriatic nail disease including both the nail plate and nail matrix region.

7.2 Methods

7.2.1 Patient groups and clinical assessment

This study was approved by the Leeds (East) Research Ethics Committee. Informed consent was obtained from all participants. A total of 86 psoriasis patients with or without PsA (169 nails) and 20 healthy controls (HC) (40 nails) were assessed for the purpose of this study.

Macroscopic nail features were assessed by clinical examination. Abnormalities including onycholysis, pits, nail plate crumbling, leuconychia, splinter haemorrhages, nail bed hyperkeratosis and red spots in the lunula were recorded and scored by using the mNAPSI scoring system (Cassell et al. 2007) by a rheumatologist experienced in this assessment. This assessor was blinded to the US findings.

7.2.2 Ultrasonography

An US scan of patients' nails was performed by a rheumatologist fully trained in musculoskeletal US (S.Z.A.), using a Logiq E9 machine (General Electric, Wauwatosa, Wisc., USA) and a linear probe at 18–10 MHz. Two nails per patient were scanned by US. The clinician performing the mNAPSI selected the most severely involved nail and the corresponding nail on the other hand (irrespective of involvement) to be scanned. The ultrasonographer was unaware of the presence or absence of nail disease and was only informed which finger was to be scanned. The nail plate and nail matrix were scanned in every patient. A thick gel layer allowed for appropriate transmission of ultrasound without any additional device.

All US assessments were performed using a multiplanar technique, scanning the nail from medial to lateral sites and from the lunula to the distal nail in order to provide as complete coverage as possible. Particular attention was paid to blind the sonographer from the clinical findings; the room was completely darkened during the US assessment and the patients and controls were asked not to talk to the sonographer prior to or during the

US assessment. The sonographer did not perform a physical examination, therefore sites other than those involved in the US scan were not seen by the sonographer. The light of the US machine alone is not enough for the sonographer to see the nails clearly.

7.2.3 Nail plate region

A dorsal longitudinal scan of the distal phalanx at the midline was used for thickness measurements. The thickness of the nail was measured as the maximum distance between the dorsal and ventral nail plates. The sonographic trilaminar appearance of the nail plate was evaluated (Gutierrez et al. 2009). The trilaminar structure (two hyperechogenic bands with a hypo/anechogenic band in the middle) was documented as either present or absent. Pits and irregularities of the nail plate surface were noted as regions where the normal convexity of the nail plate was lost (Figure 14).

7.2.4 Nail matrix region

The skin thickness was measured as the maximum thickness of the hyperechoic epidermis and hypoechoic dermis around the level of the DIP joint. The thickness of the matrix was measured as the distance between the ventral nail plate and the cortex of the distal phalanx at the level of the matrix, determined by a line perpendicular to the bone profile (Figure 15). With respect to the nail matrix region, the thickness of the extensor tendon at the level of insertion was assessed as normal or thickened by comparing it to the proximal part of the tendon. The grey-scale settings used for nail assessment were: frequency at 14 MHz, gain at 18 dB and a dynamic range at 36 dB.

Figure 14. Ultrasound appearances of nail disease

Longitudinal (A) and transverse (B) scan of the healthy nail demonstrating the trilaminar structure as two hyperechoic lines (arrows) surrounding an anechoic line. C: loss of the trilaminar appearance at the ventral plate seen as the irregularity and absence of the deeper hyperechoic line (arrow). D: pitting and irregularity of the nail plate (arrows). NP = nail plate, S = skin, DP = distal phalanx, DIPJ = DIP joint.

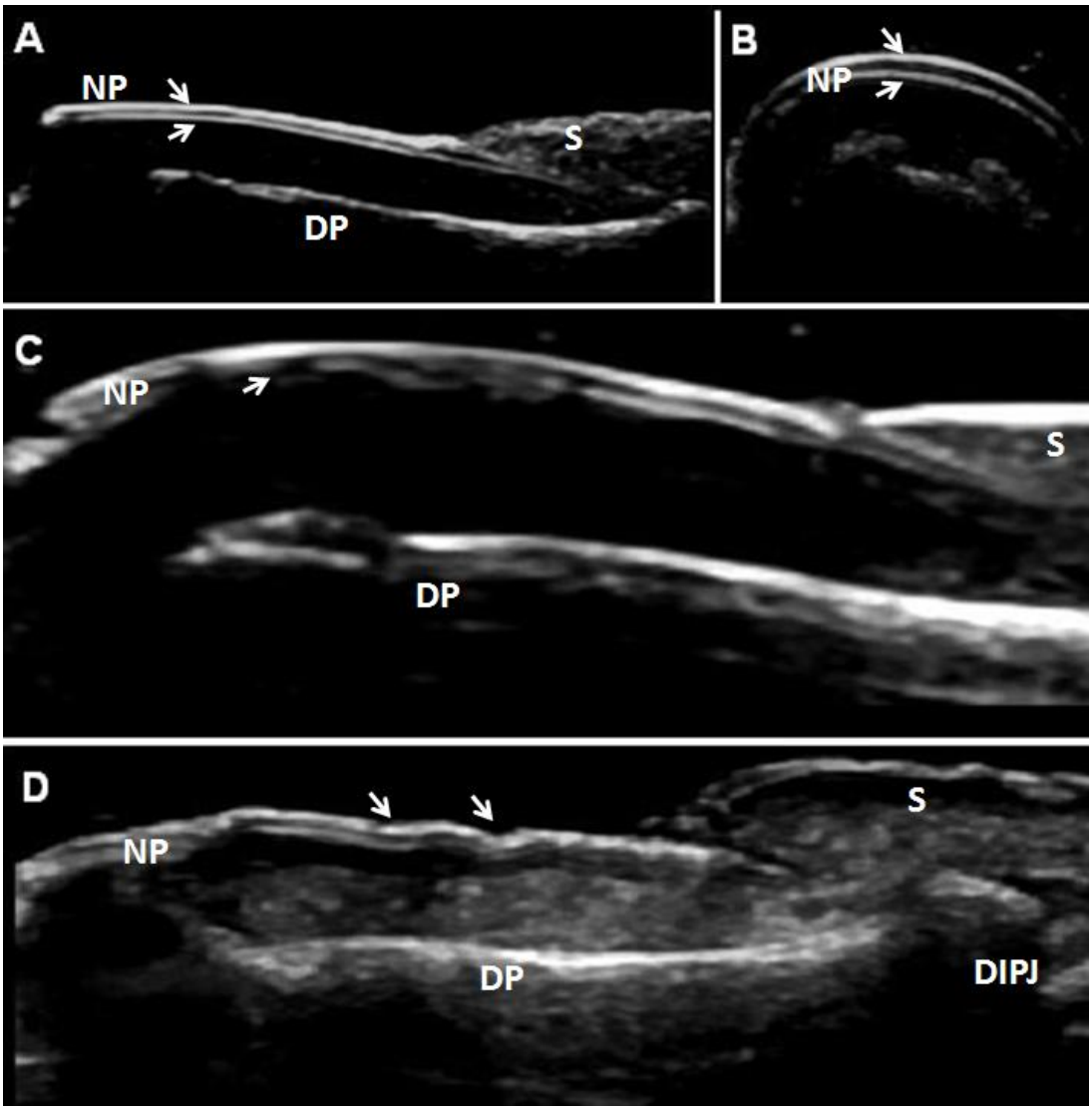
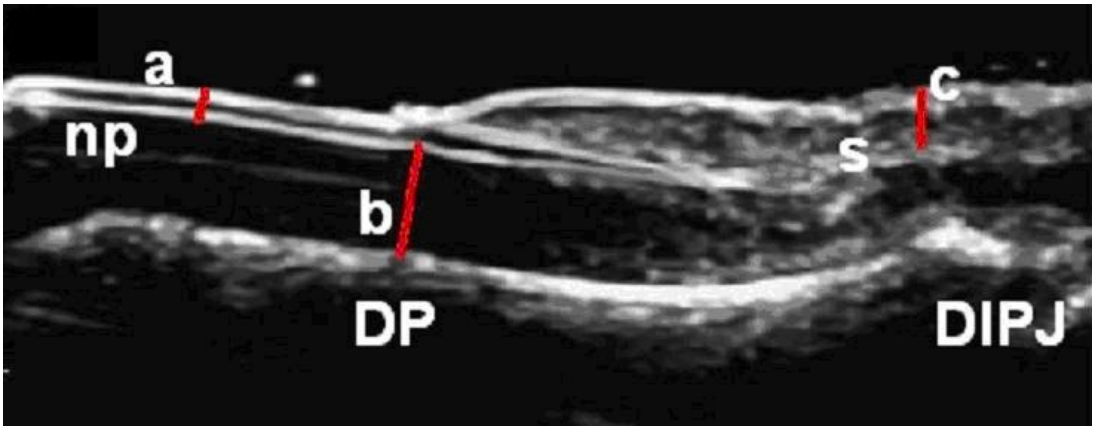


Figure 15. Thickness measurements of the nail and nail matrix

Measurements of the thickness and comparison between groups. a: nail thickness: the maximum distance between the dorsal and ventral nail plates. b: nail matrix thickness: the distance between the ventral nail plate and the cortex of the distal phalanx at the level of the matrix. c: skin thickness: the maximum thickness of the hyperechoic epidermis and hypoechoic dermis around the level of the DIP joint (DIPJ). np = nail plate, s = skin, DP = distal phalanx.



7.2.5 Statistics

Data are expressed either as frequencies or medians (range). The concordance between US and physical examination was evaluated using absolute agreements and kappa analysis and the prevalence of findings was compared using the X^2 test. The measurements of the HC and patients were compared using the Mann-Whitney U test. To test the differences between subgroups for the presence or absence of nail disease, the Kruskal-Wallis test was applied followed by the Mann-Whitney U test.

To assess reproducibility, the images of randomly chosen 100 extensor tendons were reassessed for the presence or absence of thickening by the same investigator blinded to the nail plate findings, and this revealed a moderate agreement with a kappa value of 0.58.

Statistical analysis was performed using SPSS version 11.5.

7.3 Results

Of the psoriatic patients, 33/86 (38.4%) were female, compared to 11/20 (55.0%) of the HC. 52 of the psoriatic patients (60.5%) had clinical nail disease and 42 patients (48.8%) had arthritis. Median (range) of disease duration in patients with psoriasis was 16 (1–55) months and mNAPSI score was 15 (1–56) in patients with nail disease. None of the HC had any known clinical nail disease, psoriasis nor arthritis.

7.3.1 Nail plate findings by ultrasound and comparison with clinical assessment

Patients with psoriasis had significantly more US findings of the nail than HC (42/86 [48.8%] vs. 2/20 [10.0%], $p<0.002$). There were more abnormal nail US findings in nails with clinical findings (57/101 [56.4%] vs. 6/68 [8.8%], $p<0.0001$). mNAPSI scores were higher in the presence of any nail abnormality by US (14 [0–50] vs. 1 [0–56], $p<0.0001$).

The absolute agreement between US and clinical assessment in the 169 nails of the psoriatic patients was 76.3% with a kappa value of 0.52 ($p<0.0001$). US detected abnormalities in 10 nails where clinical examination was normal. Conversely, US failed to demonstrate any lesions in 30 nails despite the presence of a positive clinical finding. These patients had either onycholysis or pitting but collectively their nails had milder abnormalities with lower mNAPSI scores than nails that were abnormal on US (mNAPSI 10 [1–56] vs. 17 [1–50], $p=0.03$).

Nail thickness was greater in patients in the psoriasis group compared to HC (0.56mm [0.3–1.9] vs. 0.5mm [0.3–0.6], $p<0.0001$). Nail thickness was higher in those nails with clinical abnormalities (0.6mm [0.3–1.9] vs. 0.5mm [0.3–0.9], $p<0.0001$).

7.3.2 Nail matrix findings

Whereas US and clinical examination were broadly similar in the assessment of the nail plate, the US assessment of the nail matrix, skin and DIP joint region was very revealing. Entheseal thickening of the extensor

tendon insertion region was more frequent in patients in whom there was an abnormality in the adjacent nail by physical examination (35/83 vs. 15/86, p=0.001). When different clinical nail findings were analysed separately, onycholysis (26/50 [52.0%] vs. 34/119 [28.6%], p=0.005), pitting (23/50 [46.0%] vs. 36/119 [30.3%], p=0.05) and nail crumbling (7/50 [14.0%] vs. 3/119 [2.5%], p=0.008) were found more frequently in patients with extensor tendon entheseal thickening. Likewise entheseal thickening of the extensor tendon insertion region was more frequent in patients in whom there was an abnormality in the adjacent nail by US, but this difference was not statistically significant (24/63 [38.1%] vs. 26/106 [24.5%], p=0.08).

Both sonographically determined nail matrix and skin thickness were higher in patients with psoriasis compared to HC (nail matrix thickness: 1.9mm [1.1–3.9] in psoriasis vs. 1.8mm [1.2–2.2] in HC, p=0.003; skin thickness: 1.1mm [0.7–1.9] in psoriasis vs. 1mm [0.6–1.6] in HC, p<0.0001). Of note, skin thickness in psoriasis was not higher in those with clinical nail disease compared to those without nail disease (Table 17). The thickness of the matrix was higher if there was clinical nail disease (2mm [1.2–3.9] vs. 1.8mm [1.1–2.5], p<0.0001).

However, with respect to the extensor tendon insertion region it was noted that tendon enthesopathy was often associated with thickening of the adjacent epidermis and oedema of the dermis (skin thickness in patients with entheseal thickening 1.2mm [0.7–1.9] compared to those without entheseal thickening 1.02 m [0.7–1.9], p=0.009) (Figure 16).

To ascertain whether the extensor tendon thickening was related to clinical DIP arthropathy or whether it could be linked to psoriasis and nail disease without clinical arthropathy, both groups were assessed separately. Patients with or without PsA had similar thicknesses of the skin, nail and matrix. Similarly, the relationship between extensor tendon thickening and clinical nail disease was seen in both psoriasis and PsA (Table 17).

Figure 16. Entheseal thickening with associated skin thickening

An example of different entheseal and skin thickness (blue line) in a HC (A) and in a patient with psoriasis (B). The thickening of the extensor tendon (red line) and enthesis is seen in addition to hypoechogenicity (*) and an enthesophyte (e) (B) as well as the increased thickness of the skin. DIPJ: distal interphalangeal joint. DP: distal phalanx, MP: middle phalanx

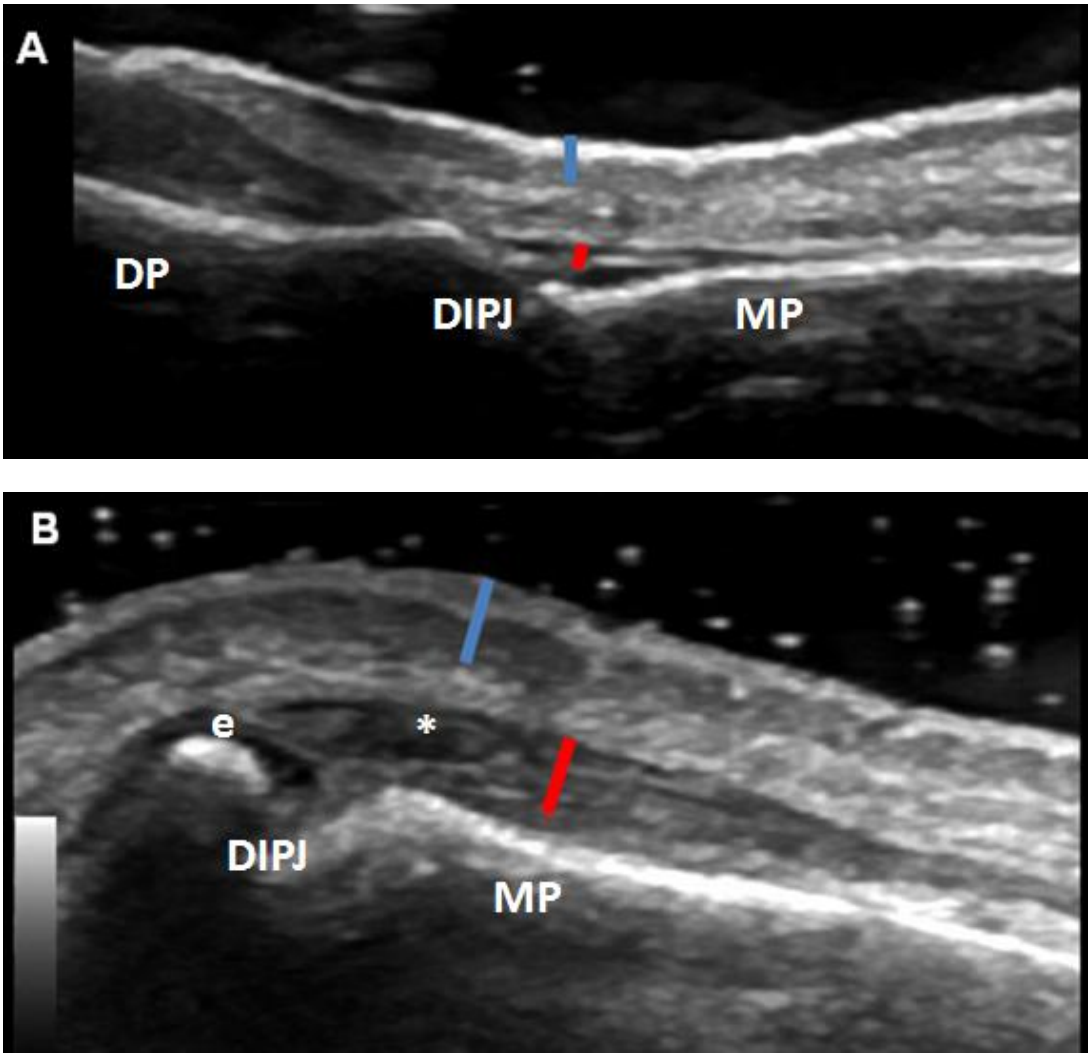


Table 17. Comparison of extensor tendon thickening, skin, nail and nail matrix thickness between different disease groups

	Psoriasis		**Psoriatic Arthritis**		**Healthy controls**
	Nail disease	**Normal nails**	**Nail disease**	**Normal nails**	
Extensor tendon thickening, frequency (%)	17 / 45 (38)	7 / 43 (16)	18 / 38 (47)	8 / 43 (19)	0 / 40 (0)
Median skin thickness, mm (range)	1.1 (0.8 – 1.9)	1.05 (0.7 – 1.7)	1.07 (0.7 – 1.7)	1.1 (0.7 – 1.9)	1 (0.6 – 1.6)
Median matrix thickness, mm (range)	1.9 (1.2 – 3.9)	1.8 (1.2 – 2.4)	2 (1.5 – 3.5)	1.7 (1.1 – 2.5)	1.8 (1.2 – 2.2)
Nail plate thickness, mm (range)	0.6 (0.3 – 1.2)	0.5 (0.3 – 0.7)	0.7 (0.4 – 1.9)	0.5 (0.3 – 0.9)	0.5 (0.3 – 0.6)

In patients with clinical DIP disease (with tenderness or swelling), extensor tendon thickening was more frequent (11/18 [61.1%] in active DIP joints vs. 39/151 [25.8%] in non-active DIP joints, p=0.005). The thickness of the skin (1.3mm [0.8–1.9] vs. 1.1mm [0.7–1.9], p=0.04) and the matrix (2.1mm [1.4–2.9] vs. 1.9mm [1.1–3.9], p=0.05) were higher in those with clinical DIP disease whereas nail thicknesses were similar (0.55mm [0.3–0.9] vs. 0.56mm [0.3–0.9], p=0.8).

7.4 Discussion

This is the first study using US to assess the entire nail apparatus including the nail plate and nail matrix region, where it is now known that the nail is integrated with the skeleton (McGonagle et al. 2009a). Both US and clinical examination were broadly similar for the assessment of the nail plate region. In the evaluation of the nail matrix region an association was noted between extensor tendon enthesopathy and nail disease. This enthesopathy was specifically associated with nail disease but not clinical PsA. In contrast, MRI was not able to demonstrate this relationship between nail disease and extensor tendon enthesopathy in psoriasis patients (Chapter 6). This likely reflects the higher resolution of ultrasound and consequently the greater ability of ultrasound to demonstrate the subtle changes seen in psoriasis patients. These findings are relevant for the development of US for the assessment of the nail disease and also point towards the importance of the enthesis in nail involvement.

These findings have implications for a better understanding of nail disease in psoriasis. The link between enthesopathy on US and clinical nail disease was not confined to pitting, a recognised matrix-specific abnormality, but was also seen with onycholysis (thought to be a nail plate lesion) which therefore would not be expected to be related to extensor tendon disease. These findings raise the possibility that nail pain and loss of function seen in the dermatological setting may in part be related to microenthesopathy-related pain. The relevance of these changes for the development of PsA and their relevance for the prognosis of nail disease awaits further study.

Another noteworthy finding of the present study was that the DIP enthesopathy was associated with both epidermal thickening and dermal oedema. This is interesting since it suggests a very close link between the pathology in the skin and the adjacent enthesis and to the best of our knowledge has not being recognised before. Perhaps the skin changes may be secondary to extension of the inflammatory processes to the adjacent dermis with secondary epidermal changes, or they may reflect common mechanical stretching responses to the skin and enthesis during finger flexion.

There are some potential limitations to this study. As with all US studies on psoriasis, it is not technically possible to be completely blinded to the skin findings if the patient has very severe disease. To attempt to prevent this situation, conversation between the patient and the ultrasonographer about their disease was avoided and the room was completely darkened from the beginning of the assessment.

In conclusion, this study confirms that US is helpful to objectively assess psoriatic nail disease and compares favourably with clinical assessment. Given that only superficial changes can be detected by physical examination, US proved to be informative in the nail matrix and adjacent extensor tendon region. In particular the US findings in this study showed a link between extensor tendon enthesopathy and nail disease. This supports the concept that nail disease in psoriasis is more than skin deep, and is linked to enthesopathy. This has broad implications for further studies into nail disease in psoriasis.

Chapter 8
Imaging of psoriatic nail disease pre and post TNF inhibitor therapy

8.1 Introduction

Nail involvement is part of the clinical spectrum of psoriatic disease. Intimate microanatomical connections have been demonstrated between the nail and the entheses around the DIP joint that might help explain the link between nail disease and arthritis (Jones et al. 1994; Tan et al. 2007).

Limited efficacy has been seen with most traditional treatments for nail psoriasis (Reich 2009). The introduction of TNF inhibitors has revolutionised the management of psoriasis and PsA, showing efficacy for psoriasis, arthritis, enthesitis and dactylitis (Ash et al. 2012a). The TNF inhibitors have also shown striking improvements in nail disease (Kavanaugh et al. 2009; Reich et al. 2010; Van den Bosch et al. 2010). Given the suggested contribution of inflammation at the adjacent entheses and bones in the pathogenesis of nail disease, it might be expected that improvements in nail disease with such therapies would be associated with dramatic resolution of the underlying arthropathic features.

Thus far the effects of anti-TNF therapies on the DIP joint in relationship to nail disease improvement have not been investigated. This study used high resolution MRI and ultrasound to investigate whether improvements in psoriasis-related nail disease correlated with improvements in underlying associated DIP joint enthesitis, bone marrow oedema like lesions (henceforth referred to as BMO), synovitis and enthesitis during TNF inhibitor therapy.

8.2 Methods

Ethical approval was gained from the local ethics committee and all participants gave written consent. Suitable cases were recruited consecutively from dermatology and rheumatology clinics. PsA cases all fulfilled the CASPAR criteria (Taylor et al. 2006). All patients were TNF inhibitor naive, but were due to commence treatment with a TNF inhibitor for either active psoriasis or PsA. To be included in this study, patients were required to have psoriatic nail disease. A full clinical and imaging assessment was performed at baseline and repeated after six months TNF inhibitor therapy.

8.2.1 Clinical assessment

Clinical assessment included the Psoriasis Area and Severity Index (PASI), Body Surface Area affected with psoriasis (BSA), modified Nail Psoriasis Severity Index (mNAPSI), 78/76 tender and swollen joint count, Spondyloarthritis Research Consortium of Canada enthesitis index (SPARCC) and a dactylitis count. Patients also reported any painful or tender nails and completed a visual analogue scale for nail pain. Quality of life was assessed using the Dermatology Life Quality Index (DLQI) (Finlay et al. 1994) and psoriasis patients also completed the Psoriasis Epidemiology Screening Tool (PEST) (Ibrahim et al. 2009). The target finger for imaging was selected on the basis of current nail disease, in addition to clinically active arthritis in that DIP joint in PsA patients.

8.2.2 Magnetic resonance imaging assessment

A high resolution MRI was performed of one finger using a 3-T Verio scanner (Siemens Healthcare, Germany). This was performed at baseline and six months. A 4cm loop coil was used to scan from the finger-tip to the middle phalanx. Gadolinium contrast was given, and Vaseline was applied to the nail to delineate the outer contour, as described by Scarpa (Scarpa et al. 2006b). Sequences performed were as described in chapter six.

The MRIs were scored by blinded paired analysis by consensus by two experienced musculoskeletal radiologists. The scoring system used has previously been reported (Tan et al. 2006a). It included anatomical structures (cartilage, collateral ligaments, flexor and extensor tendons), synovitis post-contrast and BMO on proton density / T2 weighted fat-suppressed spin echo images. Anatomical structures were recorded dichotomously as normal or abnormal. Synovitis and effusion were graded 0-2 on a semi-quantitative basis. BMO was graded from 0-3.

8.2.3 Dynamic contrast-enhanced magnetic resonance imaging

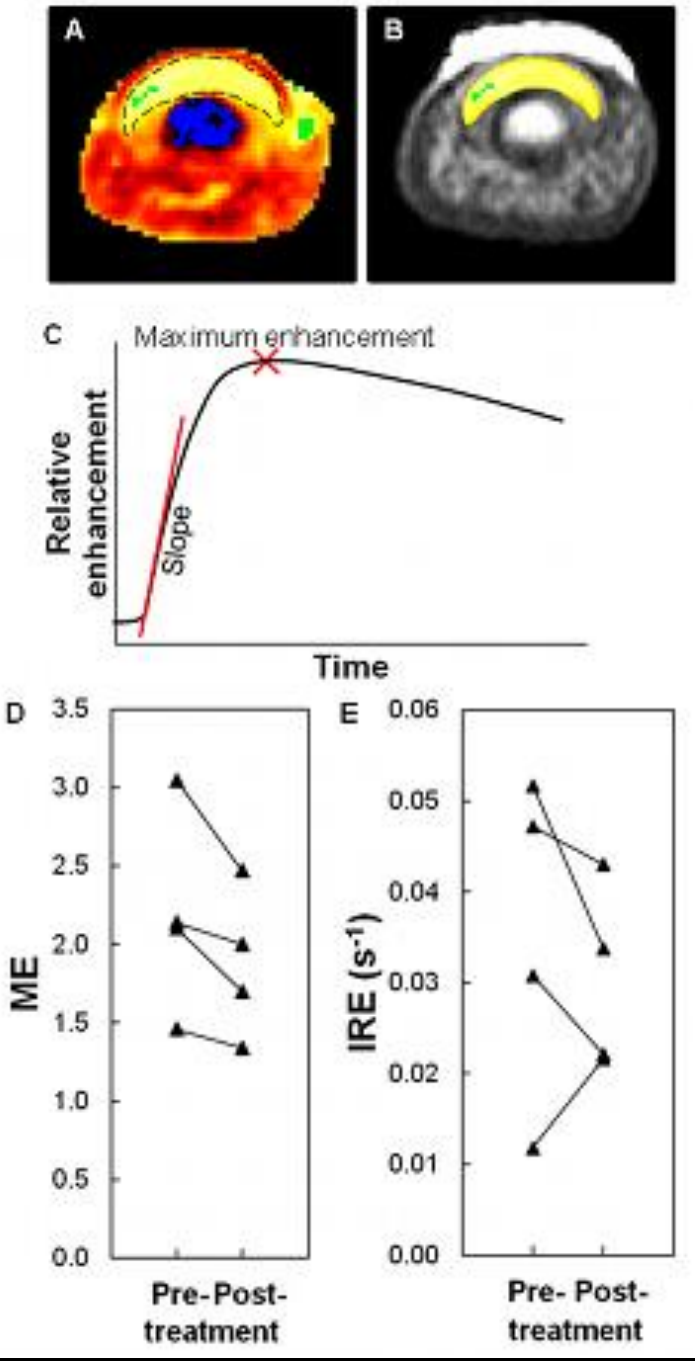
Dynamic enhancement curves were generated from regions of interest within MR images of DIP joints. DCE-MRI images were processed using a combination of in-house programmes and commercial image analysis software (Analyze10.0, Inc., Lenexa, KS). Colour-coded maps were created which reflected the temporal changes in signal intensity (Radjenovic et al. 2008; McGonagle et al. 2011b) and were used to assist the identification of regions of soft-tissue enhancement (Figure 17A). Exact regions of interest (ROIs) were manually delineated by a single investigator using these colour-coded maps (Figure 17B).

For each patient, the nail bed was observed as a high signal-enhancing, C-shaped region. Soft-tissue ROIs were selected to include the entire C-shaped region and were chosen in the most proximal slice at which this area could be seen. The median number of pixels for these ROIs was 284 (range 229–461).

Dynamic enhancement curves of signal intensity versus time were created for each ROI and quantified in terms of maximal enhancement (ME) and initial rate of enhancement (IRE) (Figure 17C) (Radjenovic et al. 2008). Owing to the small number of data (n = 4) in this preliminary study, statistical analyses were not performed.

Figure 17. Dynamic MRI images and plots

A colour-coded map for a dynamic MRI dataset of the most proximal slice at which a highly-enhanced (yellow region), C-shaped nail bed region can be seen (A). Here the ROI is outlined. The corresponding MR grey-scale image with the selected ROI superimposed (B). Note that in B, the high-signal region above the ROI is that of the Vaseline. A typical dynamic-enhancement curve; the slope represents the maximum rate of enhancement (IRE) and maximum relative enhancement (ME) is indicated as a red cross (C). Plots showing ME and IRE for all patients pre- and post treatment are shown in D and E respectively. The mean ME was 2.19 (0.65) for patients prior to treatment and 1.88 (0.48) for patients following treatment. The mean IRE was 0.035 (0.018) s^{-1} prior to treatment and 0.030 (0.010) s^{-1} following treatment.



8.2.4 Ultrasound assessment

Ultrasound of the peripheral entheses (Achilles, plantar fascia insertion, quadriceps insertions, patellar tendon origins and insertions and common extensor origins of the upper limbs) was performed and scored as described in chapters four and five (Ash et al. 2012b) with features scored according to inflammatory and chronic findings. Ultrasound of the target finger and the corresponding finger on the other hand was also performed as described in chapter seven (Aydin et al. 2012). This scan included the nail, extensor tendon, DIP joint and surrounding soft tissues.

Ultrasound scans were performed in a darkened room by a sonographer blinded to disease state. Patients were asked not to communicate with the sonographer about their diagnosis. The light from the ultrasound machine is not sufficient to see details of the skin or nails. The sonographer was asked to scan the same finger on each hand without being aware which the target finger was. Data on inter-observer reliability between the sonographers is described in chapter four (Ash et al. 2012b).

8.2.5 Statistical analysis

Results are presented as mean (SD) or median (range) depending on the distribution. Categorical data are expressed as frequencies. P values were not calculated due to the small sample size.

8.3 Results

8.3.1 Demographic data

Nine patients were recruited, with a mean patient age of 39, 7/9 patients were male. The mean duration of skin psoriasis was 19 years. Seven patients had co-existent PsA, of whom all had both tenderness and swelling of the target finger DIP joint at baseline.

8.3.2 Treatment

All patients had previously failed disease modifying therapies, as per the National Institute for health and Care Excellence (NICE) guidelines. TNF inhibitor prescription was made according to NICE guidelines and according to the choice of the treating physician. Five patients received etanercept (50mg once a week) and four patients adalimumab (40mg once a fortnight), administered subcutaneously. One psoriasis patient was withdrawn at five months due to skin non-response and was not able to attend for a repeat MRI scan. The results are presented here for the eight patients who completed the study.

8.3.3 Clinical data

Marked improvements were seen in clinical parameters (Table 18). At six months, no patients had residual clinical swelling in the target finger DIP joint and only one had persistent tenderness. Onycholysis and pitting were the most frequent abnormalities seen in the target nail at baseline (in seven and five patients respectively). The majority of patients had more than one type of nail abnormality. Three of the eight patients had completely normal nails in the target finger at six months. There was no difference in clinical nail clearance between nail matrix features (pitting or nail bed crumbling) compared to nail bed abnormalities (onycholysis, splinter haemorrhages or nail bed hyperkeratosis). Onycholysis resolved in 4/7 patients and pitting resolved in 3/5 patients. The median visual analogue score for nail pain reduced from 15/100mm to 0/100mm when excluding one patient whose score worsened because of an ingrowing toe nail at follow-up.

Table 18. Clinical and laboratory assessments.

Arthritis outcome measures reported for PsA patients only.

	Baseline	**Six months**
PASI *Median (range) (n=8)*	3 (0.2 – 22.2)	0.4 (0 – 1.9)
Swollen joint count *Mean (SD) (n=7)*	11 (6)	1 (1)
Tender joint count *Mean (SD) (n=7)*	12 (7)	1 (1)
SPARCC enthesitis index *Mean (SD) (n=7)*	3.4 (2)	0.4 (1)
mNAPSI *Mean (SD)* (n=8)	26 (15)	9 (6)
mNAPSI in the target finger *Median (range) (n=8)*	3 (2-5)	1 (0-2)
Visual analogue score for nail pain *Median (range) (n=8)*	15 (0-60)	0.5 (0-46)
Visual analogue score for global disease activity *Mean (SD) (n=8)*	60 (19)	7 (9)
DLQI *Median (range) (n=8)*	3.5 (1-29)	0 (0-3)
C-reactive protein (mg/L) *Median (range) (n=8)*	<5 in 3/8 patients 7.1 (6.4-46) in remaining patients	<5 in 7/8 patients 5.4 in remaining patient

8.3.4 Magnetic resonance imaging appearances

Baseline MRI scans showed evidence of DIP enthesitis, BMO or synovitis in all PsA patients (86%, 71% and 100% respectively). Collateral ligament enthesopathy was seen in 86%, flexor tendon enthesopathy in 71% and extensor tendon enthesopathy in 86%. The psoriasis patient had a normal MRI scan at both timepoints. The three patients with purely nail bed features of nail disease at baseline also had marked underlying BMO, synovitis and enthesitis on the baseline MRI.

Follow-up MRI scans surprisingly showed persistent inflammatory changes in the DIP joint, distal phalanx and the soft tissues around the nail. (Figure 18 and Table 19). No patient with baseline BMO showed complete resolution of this, and four of the five had no change in BMO score. All seven PsA patients had synovitis at baseline; this resolved in two, improved in one, was unchanged in three and worsened in one patient. High signal at the flexor tendon insertion was present in 5/7 patients at baseline and 2/7 patients at six months. No patient had complete resolution of extensor tendon abnormalities; BMO at the insertion resolved in two patients but was present ‘de novo’ in another at six months, peri-tendinous enhancement was present in 4/7 at baseline and resolved in two. Extensor tendon thickening as expected persisted in all patients in whom it was seen at baseline. Collateral ligament abnormalities were largely unchanged, although BMO at the proximal insertions resolved more frequently than at the distal insertions (5/6 sites resolved compared to 1/8 sites respectively).

No relationship was seen between the MRI changes and the clinical response to treatment, either in terms of the overall TJC, SJC, mNAPSI, PASI or the nail disease clearance in the target finger.

Figure 18. Nail photographs and MRI scans of a patient with PsA.

Improvements in the nail appearances are seen on the photograph. Vaseline (asterix) is seen overlying the nail on the MRI. At baseline, a large enthesophyte (periosteal new bone formation at the insertion) is seen at the extensor tendon enthesis (white arrow) with diffuse bone marrow changes (black arrow). After six months treatment with etanercept, persistent bone marrow changes are seen (black arrow), with a greater degree of synovitis.

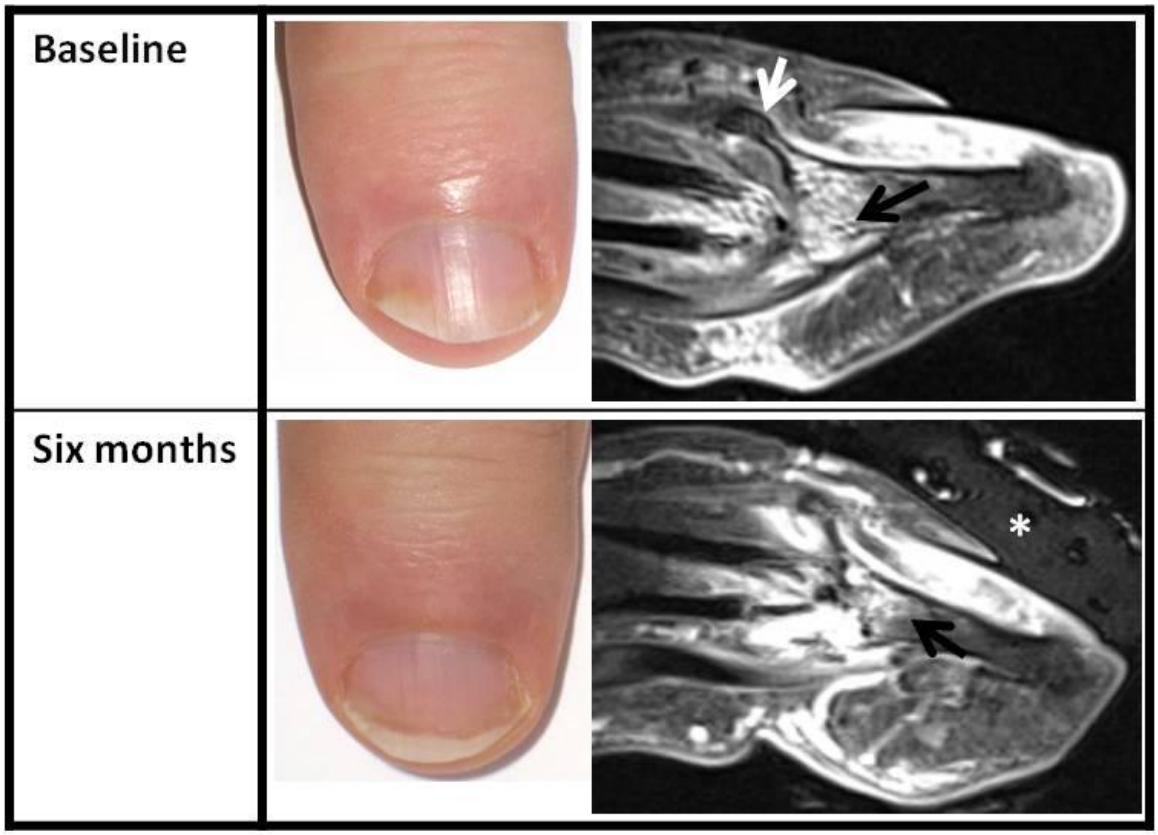


Table 19: MRI changes at baseline and follow-up for each individual patient.

Age	Diagnosis	Baseline → follow-up		Comment
		BMO score (0 – 3)	**Synovitis score (0 – 2)**	
26	PsA	0 → 0	1 → 0	No enthesitis. Synovitis resolved at F/U
49	PsA	2 → 2	2 → 2	Marked changes on both scans but overall felt to have improved.
38	PsA	3 → 3	1 → 2	Effusion resolved but more synovitis at F/U. Severe BMO on both scans
40	PsA	2 → 1	2 → 0	BMO improved but still present. Flexor tendon changes and synovitis resolved
22	Psoriasis	0 → 0	0 → 0	Normal scans
47	PsA	0 → 0	1 → 1	Persistent enthesopathy collateral ligaments and extensor tendon
54	PsA	2 → 2	2 → 2	Overall improvement on F/U scan despite persistent BMO
30	PsA	1 → 1	2 → 1	Marked improvement in collateral ligaments

8.3.5 Dynamic contrast-enhanced magnetic resonance imaging findings

Baseline and follow-up images suitable for analysis were available for only four PsA patients. The ROIs prior to, and following treatment, were analysed. ME values for all four patients were lower post-treatment, whilst IRE decreased for 3/4 patients (Figure 17D-E). These trends suggest that anti-TNF was associated with a diminution in interstitial oedema (~ME) and vascular permeability (~IRE) in the nail bed. IRE, in particular, has previously been shown to correlate with the degree of angiogenesis (Radjenovic et al. 2008).

8.3.6 Ultrasound appearances

A reduction was seen in overall ultrasound scores for peripheral enthesopathy with improvements, but not normalisation, of both inflammation and chronic change scores (Table 20).

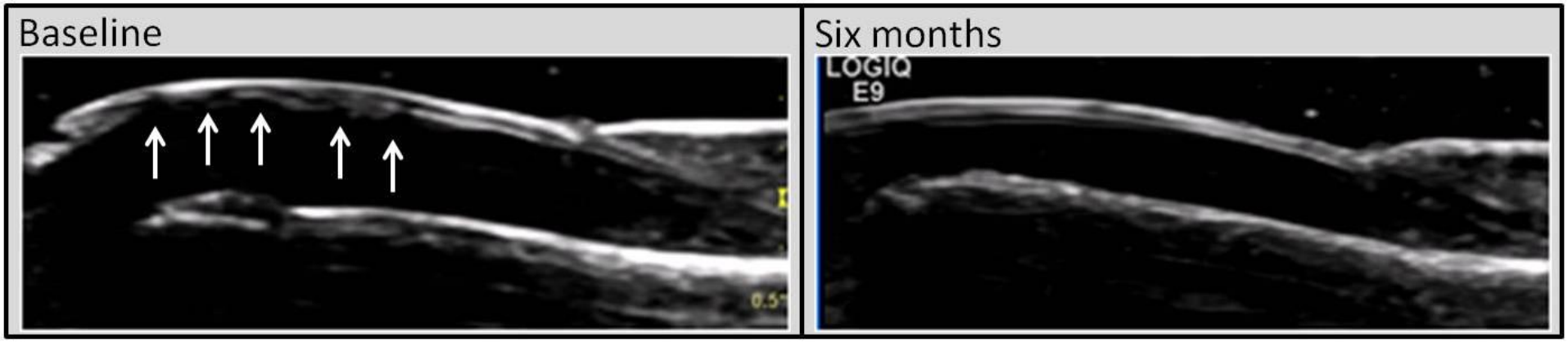
The normal trilaminar appearance of the nail was absent in 5/8 patients at baseline, of whom four patients had recovered a trilaminar appearance at follow-up (Figure 19). Pitting was seen on ultrasound in 2/8 patients at baseline and had resolved in one at follow-up, but one other patient with no pitting at baseline had pitting seen on the follow-up scan. Nail bed vascularity scores (graded 0-3 where higher values are thought to be normal) increased between baseline and follow-up in 5/8 patients, were stable in two patients and reduced in the other. Power Doppler synovitis of the DIP joint was seen in only one patient at baseline, and had resolved on the follow-up scan. Extensor tendon thickening was seen in 5/7 (71%) patients at baseline (not reported in one patient) and in 4/8 (50%) patients at six months.

Table 20. Peripheral entheseal ultrasound assessment scores

	Baseline	**Six months**
Total ultrasound peripheral enthesopathy score	27.1	21.6
Inflammation score related to power Doppler changes	1.1	0.1
Chronic enthesopathy score	11.6	9.4

Figure 19. Ultrasound appearances of the nail at baseline and after six months treatment with a TNF inhibitor

These show loss of the normal trilaminar appearance of the nail plate at baseline(arrows) with recovery of the trilaminar appearance at six months.



8.4 Discussion

Previous imaging studies have shown conflicting data regarding the resolution of inflammation with TNF inhibitors. In RA patients in remission on treatment, ultrasound has shown persistent subclinical synovitis (Saleem et al. 2009). In PsA, some studies have shown significant improvements or complete resolution of BMO with TNF inhibitors (Antoni et al. 2002; Bongartz et al. 2005; Marzo-Ortega et al. 2007a). In contrast, other studies have seen persistent BMO and synovitis after six months (Anandarajah et al. 2008; Anandarajah et al. 2010). One report described a patient with greater reductions in BMO volume at 18 months compared to six months (Anandarajah et al. 2008). In scoring the peripheral entheseal ultrasound scans, we divided findings into those related to inflammation and those due to chronic damage. This categorisation was affirmed by a recent study finding reductions in PD, bursitis and morphologic abnormality (hypoechogenicity and thickening) scores with TNF inhibitor treatment, but an increase in the calcific deposit and cortical abnormality scores (Naredo et al. 2010).

These data are limited by the small numbers of patients and, similar to other studies, the short duration of follow-up. Perhaps if the imaging had been repeated after a longer duration of treatment, a greater suppression of inflammation may have been seen. The persistent inflammation seen could relate to the high sensitivity of the imaging techniques used, although a previous high resolution MRI study of the DIP described minimal findings in healthy controls (Tan et al. 2005). Given the age of the patients and the disease duration, some of the persistent MRI changes may also relate to damage. In order to study the soft tissues around the DIP joint in detail, the scoring system previously used by Tan and Grainger was chosen in place of the PsAMRIS.

In conclusion, this pilot study assessing response to TNF inhibitors in psoriatic nail disease demonstrated persistent subclinical musculoskeletal inflammation on MRI despite good clinical response. The next step would be repeated imaging of a larger cohort of PsA patients with a longer duration

of follow-up, to demonstrate both the natural history of inflammatory lesions and whether they do indeed improve with more prolonged treatment.

Chapter 9
An assessment of high resolution magnetic resonance imaging of distal interphalangeal joint psoriatic arthritis for predicting radiographic joint destruction at nine years

9.1 Introduction

Psoriatic arthritis encompasses a diverse spectrum of phenotypes and manifestations. Pathological skeletal changes include joint ankylosis, periostitis, bone sclerosis and entheseal new bone formation, all of which can lead to disability. In the small joints of the hands and feet, PsA can also be associated with the propensity for severe osteolysis and progressive shortening of the digits, termed arthritis mutilans. Arthritis mutilans is one of the rarer subtypes of PsA, occurring in 2 – 5% of PsA patients (Torre Alonso et al. 1991; Jones et al. 1994; Veale et al. 1994). Whilst rare, it may cause major disability and thus identification of patients with arthritis mutilans at an early stage would be desirable in order to facilitate treatment.

Preliminary MRI studies have shown bone marrow oedema (BMO) (which histologically represents an osteitis (Bollow et al. 2000)) in patients with arthritis mutilans as well as other PsA subtypes (Tan et al. 2006a) (Tan et al. 2009). High resolution MRI has been used to explore the microanatomical basis for distal interphalangeal joint (DIPJ) PsA in subjects with recent onset symptoms (Tan et al. 2006a). Many of these patients had MRI-determined BMO. This study asked the question as to whether such baseline changes were associated with the evolution of destructive or disabling arthropathy at a mean follow-up duration of nine years.

9.2 Methods

The 43 patients (23 PsA as well as 10 OA and 10 healthy controls) who had participated in two previous studies (Tan et al. 2006a)(other cohort unpublished) were invited to return for a single study visit. The study was approved by the local ethics committee and all patients gave written

consent. Data were collected on the current diagnosis and current treatment as well as treatment since the previous study. Entry to the previous studies required clinician-diagnosed PsA or OA.

9.2.1 Clinical assessment

A full clinical assessment was performed, including a 78/76 tender and swollen joint count, an assessment for dactylitis and enthesitis (Leeds and SPARCCC enthesitis indices). Psoriasis was assessed using the BSA and PASI and nail disease using the mNAPSI. Inflammatory markers were measured (ESR and CRP). High resolution photographs were taken of the finger nails. Patients also completed questionnaires including visual analogue scales (VAS) for global disease activity, joint and skin disease activity and a measure of physical functioning (HAQ). For the healthy controls, in the absence of any symptoms of arthritis, only demographic data was collected and a radiograph performed.

9.2.2 Imaging assessment and analysis

One AP radiograph was taken on all patients, to include both hands. This was scored independently by two rheumatologists with an interest in the imaging of psoriatic arthritis, who were blinded to the clinical data and diagnosis. Features consistent with PsA were scored using the PsA van der Heijde modified Sharp score (van der Heijde et al. 2005). This gave a maximum possible score for the DIPJ of 9. Features consistent with osteoarthritis were scored using the Kellgren-Lawrence Grading Scale (Kellgren et al. 1957). The likely diagnosis was also recorded based on the radiographic abnormalities. Where substantive disagreement was seen between raters, these radiographs were re-scored by consensus.

The MRI scans performed as part of the previous studies were high resolution 1.5 Tesla MRI scans of one target finger. The details of the sequences have been previously reported (Tan et al. 2006a). The MRI scans were re-scored separately by two rheumatologists. The middle and distal phalanx were each divided into four quadrants and each quadrant was

scored on a semi-quantitative basis (0 – 3) for BMO. In the same quadrants, soft tissue inflammation was also scored from 0 – 3. As baseline radiographs were not available for the majority of patients, evidence of joint damage at baseline was scored from the T1 MRI sequences, recording features as per the radiographic scoring system (erosions, joint space narrowing, gross osteolysis and ankylosis).

9.2.3 Statistical analysis

To calculate the agreement between the raters for the MRI scoring, intraclass correlation coefficients were calculated for the various features using SPSS version 19. To calculate agreement for the radiographic scoring, category-specific proportions of agreement were calculated, in addition to quadratic-weighted, prevalence-adjusted, bias-adjusted Kappa (PABAK) given the non-normal distribution. This was performed using WinPEPI. Bivariate analysis with Spearman's correlation was used to correlate the baseline BMO scores with the follow-up radiographic scores. For this, the mean of the two raters scores was used.

9.3 Results

9.3.1 Demographic data

Of the original 43 patients, 18 (42%) responded to the invitation and were recruited to the study; 11/23 (48%) with PsA, 4/10 (40%) with OA and 3/10 (30%) of the healthy controls (HC). One patient originally labelled as PsA would currently be classified instead as peripheral SpA (no history of psoriasis). This patient has been included in the PsA group for the purposes of analysis.

For one PsA patient, all imaging (baseline MRI as well as baseline and follow-up radiographs) showed severe damage. Given the severe damage at baseline and difficulties in scoring the imaging due to multiple deformities, this patient has been removed from analysis and thus results for 10 PsA patients are presented henceforth.

The mean ages were 53 (PsA), 69 (OA) and 41 (HC). Of the PsA patients, 70% were male compared to none of the OA patients and 67% of the HC. The mean time elapsed since the baseline MRI scan was 9 years.

For the original MRI, in 10/17 patients the index finger was scanned, in 4/17 the middle finger was used and in 3/17 the ring finger was selected. The joint scanned was selected on the basis of active arthritis with a recent onset of symptoms.

9.3.2 Clinical data

All of the PsA (but not the SpA) patients fulfilled the CASPAR criteria (Taylor et al. 2006). 8/10 (80%) PsA patients had current psoriatic nail disease.

At the time of the visit, 7/10 (70%) of the PsA patients were taking a TNF inhibitor, 1/10 was taking NSAIDs and two were not receiving treatment for the arthritis due to inactive disease. Three of the OA patients were on no relevant medications, one was taking NSAIDs.

Prior treatment for the PsA patients had included DMARDs in 7/10 (70%), steroids in 2/10 (20%) and one each had been on a prior TNF inhibitor, NSAIDs or acitretin. One of the OA patients had previously tried sulphasalazine and one had received steroids.

For clinical features, laboratory results and patient reported outcomes see Table 21. The PsA patients generally had fairly inactive disease, which is likely to relate to the high percentage on TNF inhibitors. A high number of clinically damaged joints was seen, in keeping with the long disease duration.

Of the 10 PsA patients, two patients had arthritis mutilans clinically (only one in the joint that was scanned originally). One had complete bony ankylosis and one a flail joint in the joint scanned.

Table 21. Clinical features

	PsA N=10	**OA** N=4
Tender joint count	0 (0-5)	1.5 (0-5)
Swollen joint count	0 (0-11)	1.5 (0-2)
Damaged joint count *	5 (1-13)	12 (1-21)
SPARCC enthesitis count	0 (0-4)	0 (0)
Leeds enthesitis count	0 (0-3)	0 (0)
Number of patients with dactylitis	4 / 10	0 / 4
Duration of early morning stiffness, mins	0 (0-30)	30 (0-30)
PASI	1.2 (0-4.2)	NC
mNAPSI	8 (0-14)	NC
CRP (mg/L)	<5 in 8/10 Mean 14 in other two	<5 in all
ESR (mm/hour)	6 (2-43)	7 (6-18)
VAS global	18.5 (0-68)	NC
VAS skin	3 (0-76)	NC
VAS joints	3 (0-92)	76 (10-100)
HAQ	0.31 (0-2)	0.5 (0.5 – 0.75)

All presented as median (range). * damaged joints = bony swelling or deformity, ankylosis or arthritis mutilans. NC: not completed.

9.3.3 Imaging agreement

The ICC between the two raters for BMO scores was 0.65 (95% CI 0.27-0.85). For the soft tissue score the ICC was 0.65 (0.28-0.86).

Category-specific proportions of agreement for the radiographic scores were 82%, 71% and 59% for the erosion, joint space narrowing (JSN) and total scores respectively. Agreement analysis with PABAK for the weighted Kappa gave scores of 0.85, 0.94 and 0.92 for the erosion, JSN and total scores, respectively.

For the scoring of damage from the baseline MRI scans, category-specific proportions of agreement were 76%, 59% and 53% for the erosion, JSN and total scores, respectively. PABAK for the weighted Kappa values were 0.89, 0.69 and 0.87 respectively.

9.3.4 Magnetic resonance imaging findings

On the baseline MRI scans, all PsA and OA patients had both BMO and soft tissue inflammation. Virtually all of the PsA patients had diffuse BMO that involved the distal phalanx sometimes in its entirety. BMO scores were higher in the PsA and OA patients than in the HC, as expected (Table 22). A greater degree of soft tissue inflammation was seen in PsA than in either OA or the HC. Some mild changes (soft tissue or BMO) were seen in all the HC, suggesting that the imaging scoring may be a little too sensitive.

Table 22. Mean MRI scores for BMO and soft tissue inflammation

	PsA	**OA**	**HC**
BMO score *Mean (SD)*	12 (6)	12 (6)	2 (2)
Soft tissue score *Mean (SD)*	14 (4)	6 (3)	4 (3)

There was relatively little evidence of damage in the PsA patients on the baseline MRI scans. Seven out of 10 were either normal or had minimal JSN only, one had both erosions and JSN (this patient progressed into clinical arthritis mutilans at the time of follow-up), two had moderate to severe JSN.

Baseline MRI scans for the healthy controls showed no damage. For the OA patients, all had both erosions and joint space narrowing seen on the baseline MRI scans.

9.3.5 Radiographic findings

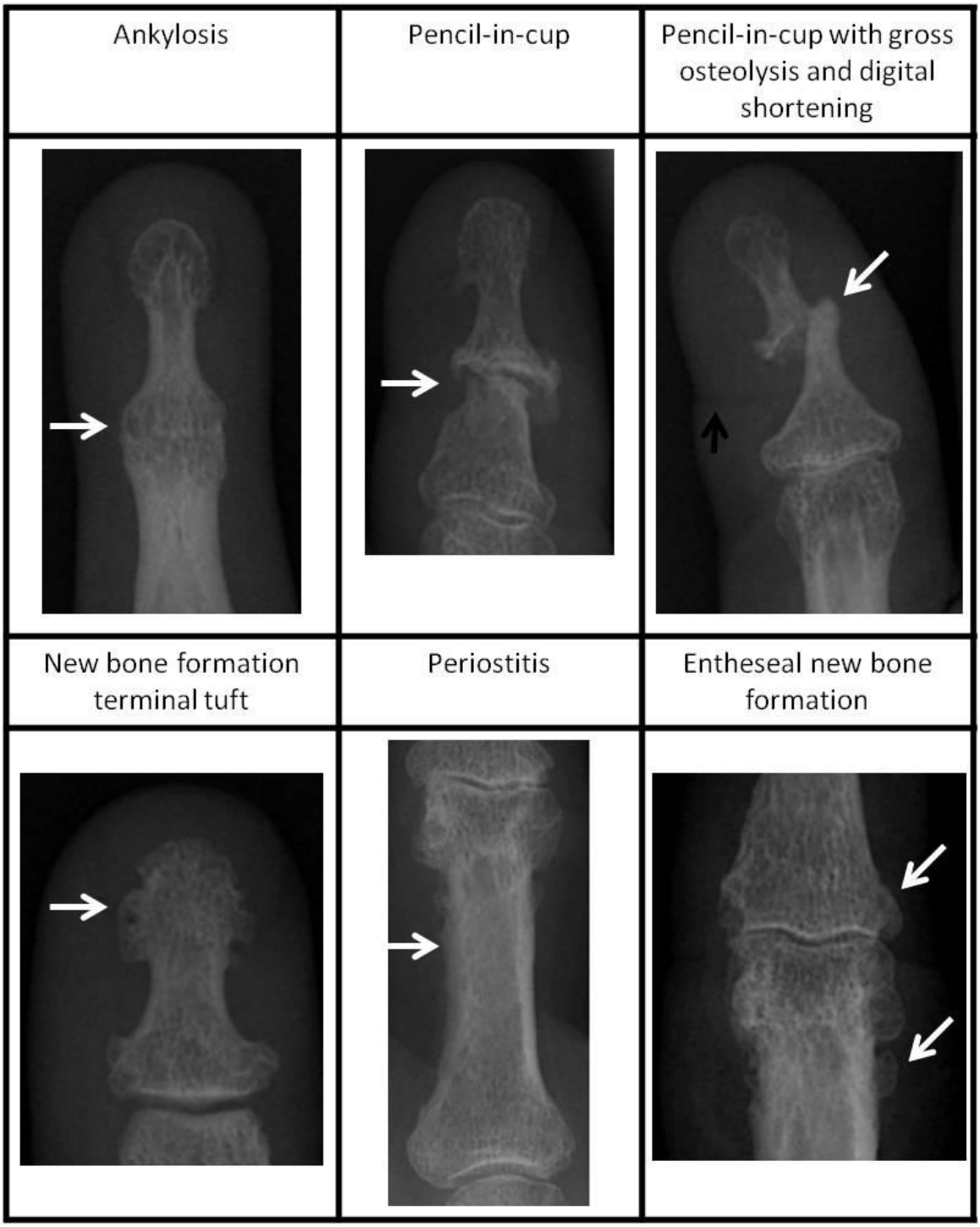
Four PsA patients had baseline radiographs available for comparison, although this was not included as part of the original studies. Two were normal, one showed minimal joint space narrowing and one showed joint space narrowing, erosions and new bone formation.

On the radiographs taken as part of the current study on PsA patients, two patients had complete DIPJ ankylosis. One out of 10 patients had DIPJ erosions and 8/10 had joint space narrowing. No patients had complete erosion both sides of the joint (as per the Marsal definition of arthritis mutilans (Marsal et al. 1999)). One PsA patient had completely normal radiographs. One had normal films apart from some terminal tuft new bone formation.

The radiographs for the OA patients all showed either grade 3 or grade 4 changes on the Kellgren-Lawrence score. The scorers were able to identify correctly the features as consistent with OA in all cases. The radiographs for the healthy controls were entirely normal in two and showed minimal joint space narrowing in one slightly older subject.

Figure 20. Examples of different radiographic findings

Digital shortening can be seen with folds of redundant skin (black arrow). Example images presented here may not be the joint that was scanned as part of the MRI study.



9.3.6 Association between bone marrow oedema and arthritis mutilans

The three patients with clinical arthritis mutilans, flail joint or ankylosis in the joint scanned all had severely abnormal current radiographs (Table 23).

Table 23. Imaging results for patients with severe radiographic abnormalities

	PsA with arthritis mutilans, flail joint or ankylosis in joint scanned N=3	**Non-mutilans PsA N=7**
BMO score at baseline *Mean (SD)*	17.8 (1)	12.1 (6)
MRI erosion score at baseline *Mean (SD)*	1 (2)	0 (0)
MRI JSN score at baseline *Mean (SD)*	0.7 (1)	0.8 (1)
Total radiographic score at follow-up *Mean (SD)*	3.7 (1)	1.4 (1)

A moderate degree of correlation was seen between the baseline BMO score and the follow-up total radiographic score in PsA patients; correlation co-efficient 0.519 (p=0.125) (Figure 21)

Figure 21. Correlation of baseline BMO score and follow-up radiographic score for PsA patients

Note that one patient is excluded as detailed in the results, section 9.3.1.

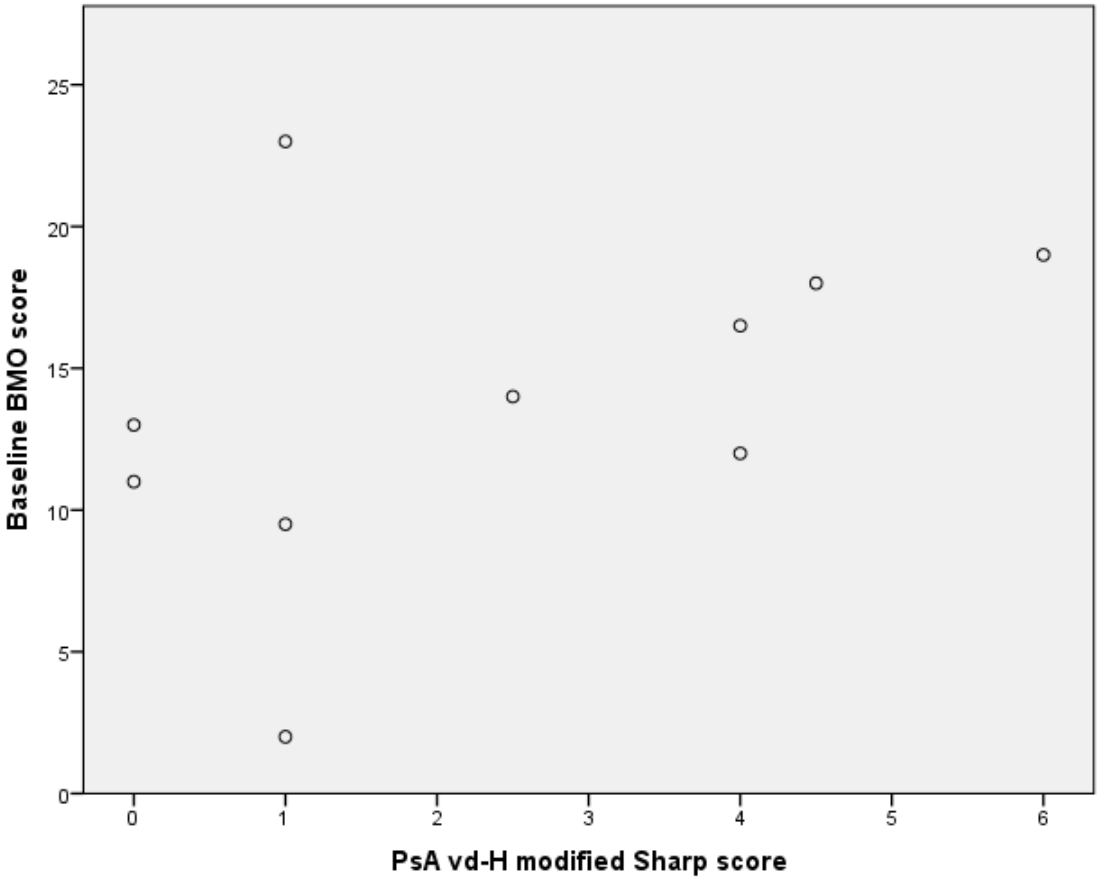


Table 24. Radiographic findings for the PsA patients

Age	**Baseline x-ray features (where available)**	**Baseline MRI ***				**Current PsA treatment**	**How long TNF started after MRI**	**Clinical features**	**Current x-ray features**
		Inflammation score		**Damage score**					
		BMO score	**Soft tissue inflammation score**	**Erosion score**	**JSN score**				
47	Minimal JSN	14	11	0	0	None	N/A	Bony swelling	Moderate JSN
51	-	9.5	9	0	0.5	None	N/A	Bony swelling	Minimal JSN
64	-	18	11.5	3	1.5	Etanercept	7 years	Mutilans	Marked JSN
65	One erosion, moderate JSN	12	15.5	0	2	Etanercept	1 year	Normal	Marked JSN, periostitis, one erosion
43	-	2	16	0	0	Etanercept	3 years	Normal	Minimal JSN
64	-	23	22	0	3	Etanercept	2 years	Bony swelling	Minimal JSN
60	Normal	11	7.5	0	0	Etanercept	7 years	Normal	Normal

Age	Baseline x-ray features (where available)	Baseline MRI *				Current PsA treatment	How long TNF started after MRI	Clinical features	Current x-ray features
		Inflammation score		Damage score					
		BMO score	Soft tissue inflammation score	Erosion score	JSN score				
36	-	19	16	0	0.5	Etanercept	7 years	Ankylosis	Ankylosis
44	Normal	13	15	0	0	Indomethacin	Had one year of etanercept, 2 years after MRI	Normal	Normal
55	-	16.5	18	0	0	Adalimumab	7 years	Flail joint	Ankylosis

*For the baseline MRI mean scores for the two raters are given.

9.4 Discussion

This is the first long-term follow-up of PsA DIP joint cases with a baseline MRI scan available. These findings did not show a definite link between baseline bone oedema status and subsequent joint damage. This may be due to the fact that all the cases had bone oedema at baseline. It was not possible to follow the progress of a single BMO lesion due to the diffuse nature of the BMO seen at baseline.

A high proportion of the patients were receiving treatment with a TNF inhibitor at the time of follow-up. Bone oedema has been shown to resolve rapidly with TNF inhibitor treatment (Bongartz et al. 2005) and in PsA TNF inhibitors are known to be potent suppressors of radiographic progression.

It was interesting to note that baseline bone oedema was associated with a disparate group of radiographic outcomes nine years later which included both osteolysis and new bone formation. Joint space narrowing was the most common feature overall, which may relate to secondary osteoarthritis due to the time since the previous imaging and the age of the study participants.

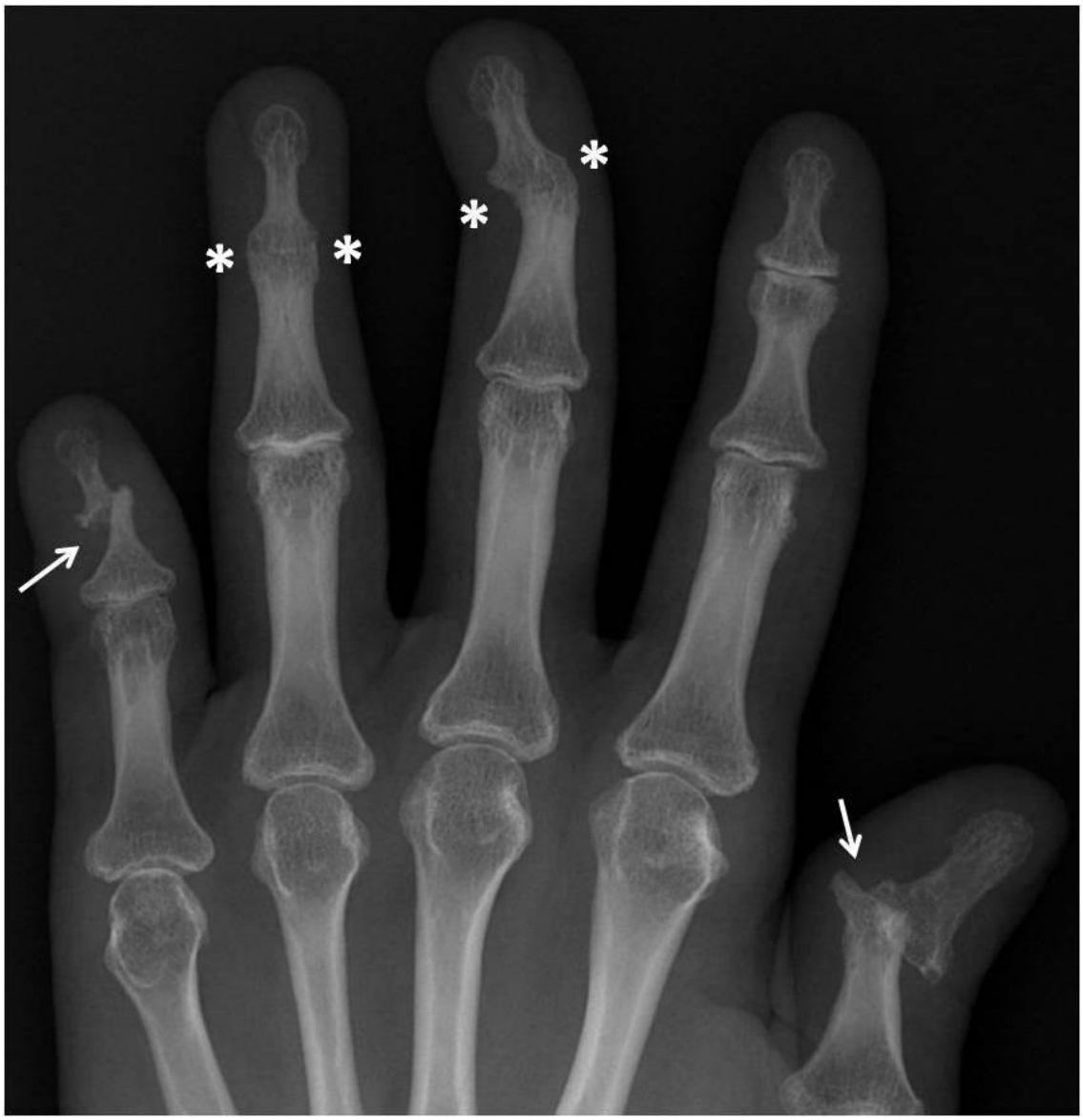
A significant limitation of this study is the low recruitment rate and small number of patients. The follow-on study was not planned at the outset and therefore patients were not expecting to be recalled. Recruitment may also have been limited by the fact that some patients from the original cohorts were recruited and seen at a rural hospital 23 miles away from the inner city hospital where the follow-up visits took place and thus patients may not have been keen to travel for the study visit. Some time had also elapsed and thus patients may have been limited by health problems or infirmity.

In an ideal setting, this study would have a much larger number of participants with complete follow-up data available. A treatment-naive population would be studied in order to not influence the radiographic progression. Furthermore, interval data on clinical course in terms of episodes of swelling would be recorded as this is known to predict damage.

On balance these preliminary findings do not support the use of MRI in prognostication as the outcomes were variable in the presence of severe

baseline bone oedema. This may have been due to the efficacy of treatment but this is not something that can be addressed, as it would be unethical to withhold treatment from subjects with early arthritis purely to define the disease natural history. Despite the fact that patients were treated there was still a surprising degree of radiographic progression in this small cohort.

Figure 22. Both ankylosis (*) and osteolysis (arrows) in the same PsA patient



Chapter 10
Discussion and future directions

In a time of evolving new biologic treatments targeting different parts of the immune system, an understanding of the underlying pathogenesis of a disease as varied as PsA is vital. This enables physicians to target treatments appropriately both in terms of predictors of disease severity but also for different disease subtypes.

The work in this thesis expands on and proceeds from previous work performed in Leeds, focussing on the role of enthesitis in the pathogenesis of psoriatic nail disease.

10.1 Enthesitis in psoriasis patients

It has been known for some time that nail disease is more common in PsA than in psoriasis, and that in fact nail disease predicts the future development of PsA amongst psoriasis patients (Wilson et al. 2009a). The results in chapter 4 show that psoriasis patients with nail disease do have a greater degree of enthesitis at the peripheral entheses than psoriasis patients with normal nails. These results suggest that nail disease may be a clinical marker for underlying subclinical musculoskeletal inflammation, and may henceforth explain why it is a predictor for PsA development. Following on from here, it raises the question as to whether the presence of nail disease may be used to sub-select a population at higher risk of developing PsA, and the use of ultrasound in this cohort may again allow a greater predictive value. Preliminary data from a group in Italy does suggest that a higher GUESS score in psoriasis patients predicts the development of PsA, but this requires further study in a larger cohort for confirmation (Tinazzi et al. 2011).

Our findings also echo those of other groups, finding that minor entheseal abnormalities are common even in healthy controls, and one of the key challenges of ongoing research in this field is to differentiate between

‘normal’ findings and those which are truly pathological, without reducing the sensitivity excessively.

Even then, some of these chronic findings were more common in psoriasis patients than healthy controls, suggesting that even asymptomatic psoriasis patients without arthritis may have aberrant healing responses to mechanical stress at the entheses.

As an alternative approach, a number of screening questionnaires have been developed for the identification of undiagnosed PsA amongst psoriasis patients. The CONTEST study has now compared three of these in a head to head study; PEST, PASE and ToPAS (Coates et al. 2013). The sensitivity and specificity for each questionnaire was lower than in their original validation studies. Each questionnaire gave a sensitivity of around 75%, but with a specificity of 30 – 39%. The low specificity reflects a high number of ‘false positive’ results with the questionnaires, largely due to osteoarthritis.

A separate study assessed the same screening questionnaires again in a secondary care population but with some differences in study design (Haroon et al. 2013). Contrasting results were found, with all questionnaires showing a low sensitivity (24 – 41%) and a high specificity (90 – 98%). It was notable that the screening questionnaires performed better in identifying polyarticular PsA than axial, oligoarticular or entheseal disease. These questionnaires therefore may be useful in helping dermatologists identify patients who may have PsA in order to refer for rheumatological assessment. However, their use will be limited by the lower sensitivity in non-polyarticular PsA and the low specificity, meaning that they will identify a number of patients with other musculoskeletal conditions such as OA.

10.2 Differences in enthesitis between psoriatic arthritis and psoriasis patients

In chapter 5 differences between the enthesitis in PsA and in psoriasis are described. The presence of power Doppler was much more frequent in PsA than psoriasis, as were other inflammatory features of enthesopathy (hypoechogenicity, entheseal thickening and bursal enlargement). This

suggests that the nature of enthesopathy may differ between psoriasis and PsA.

In our study, PD signal at the enthesis was seen in 9.5% psoriasis patients but not in the control subjects. In keeping with this, in a study recently published by Naredo et al. (Naredo et al. 2011), PD was seen in or around the enthesis in 11% psoriasis patients and no healthy controls. The authors analysed demographic and clinical factors between those psoriasis patients with and without entheseal PD signal and found a higher mean age in those with PD but no difference in the severity of the psoriasis or other demographic or clinical factors. A further study in 45 psoriasis patients and 45 healthy controls also found no PD signal in healthy controls, but found PD in 0.9% of the entheses assessed (Gutierrez et al. 2011a).

This raises the question as to whether when assessing the predictive value of entheseal ultrasound in psoriasis patients, some features may be of more value (such as power Doppler) while other findings (such as enthesophytes and calcifications) may lack specificity. Thus it may better to use certain features in place of a total score. Another factor to bear in mind is that entheseal ultrasound scores have been shown to be higher in males than females and therefore a single cut-off score would not be appropriate for both groups (de Miguel et al. 2011b).

10.3 Imaging of the nail and distal interphalangeal joint in psoriasis patients

With MRI in chapter 6 we were able to reproduce the relationship previously seen between nail disease and extensor tendon enthesitis in PsA patients. However, we were not able to demonstrate an association between DIPJ enthesopathy and nail disease in psoriasis patients. Subtle evidence of inflammation was seen, but not frequently, and without any real relationship with nail disease. The data also suggest that there may be a relationship also between flexor tendon inflammation and nail disease in PsA, which is plausible as fibres from the flexor tendon do wrap around the distal phalanx to anchor in the vicinity of the nail bed. A recent study using positron emission tomography (PET) found diffusely increased update in the distal

phalanx in PsA patients, but with particular uptake noted at the entheses, periosteum and tufts (Tan et al. 2013). This fits with previous research showing that fibres from the extensor and flexor tendons merge with the periosteum (Tan et al. 2007). This relationship bears further study. Using the high resolution finger coil, good images of psoriatic nail disease were obtained, also demonstrating thickening of the nail bed in some patients with severe nail disease.

Using ultrasound in chapter 7 however, a relationship between nail disease and extensor tendon thickening was demonstrated in psoriasis patients. The resolution of the ultrasound probe was higher than with the MRI scan and thus it may be that the MRI is not sufficiently sensitive to detect the subtle inflammation seen in psoriasis patients. High resolution ultrasound is able to assess entheseal fibrocartilage, which is only 0.5mm thick, while the slice thicknesses for the MRI scans used in the study were 1.3 – 1.5mm, with a resolution of 512x358 pixels on the sagittal images.

The results also show that ultrasound is a feasible alternative way to assess psoriatic nail disease, being able to demonstrate a number of features including pitting, nail bed hyperkeratosis and nail thickening. The finding of thickening of the overlying dermis and epidermis in subjects with extensor tendon enthesopathy was not expected. Further study of this may be better performed using OCT, where objective measurements of nail thickness are possible, including responsiveness to change (Sattler et al. 2012). Our group has also recently reported a case of psoriatic nail disease assessed using OCT (Aydin et al. 2011). The OCT gives a far higher resolution than ultrasound and thus the ability to study abnormalities within and beneath the nail plate as well as measuring the skin thickness accurately.

Looking at PsA-related nail disease, a study has been reported on 34 patients with PsA (Dalbeth et al. 2012). All underwent a baseline clinical assessment and MRI examination of the dominant wrist and fingers. At baseline, an association was seen between onycholysis and hyperkeratosis and MRI evidence of bone erosion and proliferation. One year later, twenty patients had a repeat clinical assessment. The study found that nails which developed hyperkeratosis or onycholysis by the time of follow-up were more likely to have had bone marrow oedema on the baseline MRI. This is

counter to what would be expected, as both of these features are traditionally thought to be nail bed related, most likely due to psoriatic plaques under the nail. The numbers are small, with only four nails developing each feature. The study does support the idea of underlying musculoskeletal inflammation being important in the pathogenesis of psoriatic nail disease, but is limited by the small numbers.

10.4 Response of nail disease and underlying musculoskeletal inflammation to biologic therapies

The efficacy of TNF inhibitors in treating psoriasis, psoriatic arthritis and associated nail disease is already proven. The study described in chapter 8 aimed to assess instead the underlying DIPJ bone and soft tissue changes in patients undergoing such treatment. The results are limited by the small numbers, but the presence of persistent imaging-detected inflammation at both the entheses and the joint after six months treatment is surprising in the context of good clinical response.

These results are however similar to a recent study assessing the response to adalimumab in PsA patients using MRI scanning of a symptomatic wrist or knee (Anandarajah et al. 2010). Baseline and follow-up scans were available for 11 patients. The BMO and joint effusion scores showed marked improvements, but the joint erosion score increased during treatment. Persistent BMO was seen in the majority of patients after six months treatment and the overall synovitis score did not change. Does this persistent imaging evidence of inflammation matter? This remains to be seen, in view of the fact that TNF inhibitors are known to inhibit radiographic progression effectively. It may be that the imaging response lags behind clinical response and will resolve fully with further time on treatment.

Dynamic contrast-enhanced MRI is an emerging technique for the assessment of vascularity in tissues. As this was incorporated into the study only partway through, results were available for only four patients but these do show some promise and suggest that it may be a useful technique for assessing angiogenesis in these areas.

The findings in the peripheral entheses seen with ultrasound also show persistence. Unsurprisingly the inflammation score improves more than the chronic enthesopathy score, which would not be expected to improve as much with treatment (Naredo et al. 2010). In contrast, a recent longitudinal study in early SpA found that a number of erosions at the Achilles enthesis had disappeared by the time of follow-up ultrasound scans (de Miguel et al. 2011a), suggesting that these are not necessarily permanent structural lesions. One possibility raised by the authors is that new bone formation occurs with time, and this may be responsible for the resolution of the erosions.

We found an increase in nail bed vascularity during treatment and with an improvement in clinical nail disease. Using the nailfold resistance index to study the vascularity of the proximal third of the nailbed, it has recently been suggested that psoriatic nail disease is associated with a pathologically decreased blood flow in the nail bed (Husein El-Ahmed et al. 2012). The authors postulate that this may relate to endothelial cell dysfunction. This then might be expected to improve with treatment, as the results in chapter 8 suggest. This may therefore have significant implications for microvascular disease elsewhere, which is important in patients who are known to be at increased risk of accelerated vascular disease.

10.5 Long term outcomes of distal interphalangeal joint bone marrow oedema in psoriatic arthritis

In the long-term follow-up of two cohorts of PsA patients with DIPJ arthritis (chapter 9), a high proportion of these patients with BMO at baseline were on TNF inhibitors at follow-up. This clearly influences radiographic progression, but despite this the majority of patients had joint space loss and some had developed arthritis mutilans or ankylosis in one or more digits. This is a limitation of observational studies in that many other confounding factors may alter the findings. It is still unknown as to why new bone formation occurs in one joint while osteolysis occurs in another within the same patient.

Given the efficacy of TNF inhibitors, these are likely to be given more readily by clinicians to patients with severe disease and the prevalence of arthritis mutilans may well reduce over the next ten years.

10.6 Future directions

One of the most important questions is the predictive value of subclinical ultrasound enthesitis in the later development of PsA. If this can be established, then the next stages are to consider whether screening should be performed and whether treatment is indicated at this stage. This echoes ongoing research in RA, where family and population studies show that patients with a positive ACPA (anti-citrullinated protein antibody) can be identified at a pre-clinical stage. In RA, early treatment may be beneficial both for preventing structural damage and as there is a far greater chance of achieving remission (Emery et al. 2012).

Larger studies with a longer duration of follow-up are needed to perform ultrasound scans on asymptomatic psoriasis patients without arthritis, to clarify whether ultrasound evidence of enthesopathy does predict the later development of arthritis, and if it does, to identify any other predictive features and to develop a model with the best predictive value. The patients in our study most frequently had plaque psoriasis (the most common phenotype) but it would also be important to establish whether subclinical enthesopathy is also seen to the same degree in palmar-plantar, flexural, guttate and pustular psoriasis. The location of psoriatic plaques may also be relevant, as suggested by the article by Wilson et al. finding an increased risk with scalp and inter-gluteal psoriasis (Wilson et al. 2009a).

Identifying patients at risk of PsA would aid both in closer monitoring but also potentially in helping dermatologists choose appropriate treatments which help the joints as well as the skin (for example methotrexate rather than acitretin or UVB). There are currently no data available on the efficacy of TNF inhibitors or other biological drugs in treating asymptomatic enthesitis in psoriasis patients but it may be that effective treatment at this stage alters the disease course and averts the development of arthritis. Certainly treatment at an early stage may help prevent joint damage forming.

However, it is a fine balance between the benefits of treatment and the risks of screening causing psychological morbidity and the risk of unnecessary treatment if the predictive model does not allow accurate prediction of those who will develop PsA. In the mean time, we should focus on better identification of psoriasis patients with undiagnosed PsA using one of the number of questionnaires available for this.

The validation of ultrasound against clinical examination for the assessment of psoriatic nail disease opens doors for further use in studies. However, clinical examination is likely to remain the main tool for use in clinical trials due to its better feasibility. Ultrasound does however seem more effective at imaging the extensor tendon than MRI. The research in this thesis still does not answer the questions as to whether DIPJ enthesopathy plays a role in the pathogenesis of nail disease in psoriasis patients (without arthritis). Ultrasound may be the best tool to further study this. One other potential aspect for study is whether the different types of psoriatic nail disease are of different pathogenesis. In the study in chapter 7 it was difficult to tease this out, largely because the majority of patients had both ‘matrix’ and ‘nail bed’ types of nail lesion. A larger study recruiting patients with purely one type of nail lesion (only pitting or only onycholysis) may be better able to answer such questions, but recruitment may be difficult.

Optical coherence tomography (OCT) is a new technique that is showing promise in the assessment of nail disease amongst other areas. Using OCT, accurate measurements of the nail thickness may be recorded, which appear sensitive to change and thus may allow a more objective tool for future use in research (Sattler et al. 2012).

The preliminary work done in assessing underlying musculoskeletal inflammation and the response of this to TNF inhibitors in patients with psoriatic nail disease is limited by the very small numbers. A future study would need to be larger, with a more pure patient population of only patients with PsA. Different drugs may also have different efficacies (as seen with the TNF inhibitors and their varying efficacy on skin psoriasis). A longer duration of follow-up would allow evaluation for whether the persistent inflammation seen at six months is simply slow to resolve or whether this persists in the longer term.

Studies assessing patients with arthritis mutilans and other severe phenotypes are difficult due to the rarity of these patients. Perhaps the most important research currently is in predictive factors for the onset of arthritis mutilans and in demonstrating the efficacy of treatment in these patients, in order to facilitate greater access to treatments for patients such as this with severe disease.

10.7 Review of hypotheses

Nail disease could be a marker for those psoriasis patients who have subclinical enthesitis elsewhere, and therefore could be a potential predictor for the later development of PsA.

The results presented in chapter four show that psoriasis patients with nail disease do indeed have a higher median ultrasound enthesitis score than psoriasis patients without nail disease. This would lend support to this hypothesis; that nail disease may be associated with a greater degree of subclinical enthesopathy. Further prospective studies are still needed to fully establish the relationship between subclinical enthesitis in psoriasis patients and future arthritis development. Ultrasound evidence of enthesopathy was very common (including in healthy controls) and one of the challenges for the future is therefore to assess which ultrasound findings may be the most predictive for future arthritis development.

Nail disease is due to subclinical or clinical enthesitis around the DIP joint in both PsA and psoriasis.

The relationship between nail disease and DIP joint arthritis and enthesitis in PsA patients was again seen in the studies presented in chapters six and seven. In psoriasis patients, although subtle evidence of DIP joint enthesopathy was seen with MRI, no relationship was found between this enthesitis and the presence of nail disease. Ultrasound scans were better able to visualise the extensor tendon insertion and using ultrasound, an association was seen between nail disease and extensor tendon thickening in both psoriasis and PsA. Given that different patterns of nail disease may represent different pathological processes, this still requires further evaluation, ideally in cohorts of patients with sub-group analyses for the pattern of clinical nail disease.

The improvement in nail disease seen with anti-tumour necrosis factor (TNF) therapy may be due to improvements in enthesitis around the DIP joint.

This hypothesis was not confirmed by the results presented in chapter eight. Improvements in clinical nail disease were seen, along with good efficacy for psoriasis and arthritis clinically. With ultrasound scans looking at enthesopathy at the heel, knee and elbow, residual findings were mainly the chronic features of enthesopathy. MRI scans of the DIP joint however showed persistent inflammation within the joint and surrounding entheses. Data from other studies support the fact that imaging evidence of inflammation may persist despite clinical improvement. It is currently unclear whether this persistent inflammation should be a cause for concern; whether it may lead to more long term joint damage or is there simply a time lag between clinical and imaging improvement.

DIP joint bone marrow oedema lesions in active PsA are predictive of radiographic damage in that joint at a later stage.

This hypothesis could not be tested using the available data in chapter nine largely because bone marrow oedema was such a common and widespread feature in the baseline MRIs. It was therefore not possible to either follow the progress of a single bone marrow lesion or compare joints with and joints without bone marrow oedema. The majority of patients were receiving anti-TNF agents at the time of follow-up, which have a significant effect on reducing radiographic progression and will have altered the results of the study. Joint space narrowing was the most common feature seen at the time of follow-up.

Chapter 11
Conclusions

This thesis aimed to provide an explanation for the predictive value of clinical nail disease in psoriasis for the later development of PsA.

Limited data were found to support the concept that nail disease in psoriasis is due to subclinical DIPJ enthesitis. This may relate to different nail phenotypes having different pathological causes.

Nail disease does however appear to be a marker for subclinical enthesitis globally. A combination of the presence of clinical nail disease and ultrasound scans of the entheses may offer potential for better identification of psoriasis patients at high risk for developing PsA.

Nail disease clearly does respond to TNF inhibitors, but persistent inflammation is seen in and around the DIPJ in PsA patients, suggesting that imaging improvements may take longer to occur than clinical response.

A small cohort of patients with active DIPJ arthritis with diffuse bone marrow oedema on a baseline MRI scan did show radiographic damage including joint space loss after nine years follow-up, but the assessment of this is complicated by confounders including treatment.

Identifying patients with PsA at an early stage remains a challenge, but increasing awareness amongst dermatologists, the development of screening questionnaires and further validation of ultrasound in these patients will play a key role in the future.

List of References

Abe, M., T. Syuto, et al. (2011). "Improvement of quality of life and clinical usefulness of cyclosporin administration in patients with nail psoriasis." The Journal of Dermatology **38**(9): 916-918.

Abu-Shakra, M., D. D. Gladman, et al. (1995). "Longterm methotrexate therapy in psoriatic arthritis: clinical and radiological outcome." The Journal of Rheumatology **22**(2): 241-245.

Abuzahra, F., F. Spoler, et al. (2010). "Pilot study: optical coherence tomography as a non-invasive diagnostic perspective for real time visualisation of onychomycosis." Mycoses **53**(4): 334-339.

Aktan, S., T. Ilknur, et al. (2007). "Interobserver reliability of the Nail Psoriasis Severity Index." Clinical and Experimental Dermatology **32**(2): 141-144.

Alcalde, M., J. C. Acebes, et al. (2007). "A sonographic enthesitic index of lower limbs is a valuable tool in the assessment of ankylosing spondylitis." Annals of the Rheumatic Diseases **66**(8): 1015-1019.

Alenius, G. M., E. Berglin, et al. (2006). "Antibodies against cyclic citrullinated peptide (CCP) in psoriatic patients with or without joint inflammation." Annals of the Rheumatic Diseases **65**(3): 398-400.

Alenius, G. M., E. Jidell, et al. (2002a). "Disease manifestations and HLA antigens in psoriatic arthritis in northern Sweden." Clin Rheumatol **21**(5): 357-362.

Alenius, G. M., B. Stenberg, et al. (2002b). "Inflammatory joint manifestations are prevalent in psoriasis: prevalence study of joint and axial involvement in psoriatic patients, and evaluation of a psoriatic and arthritic questionnaire." The Journal of Rheumatology **29**(12): 2577-2582.

Alibert, J. L. (1818). Precis theoretique et pratique sur les maladies de la peau. Paris, Caille et Ravier.

Allen, M. H., H. Ameen, et al. (2005). "The major psoriasis susceptibility locus PSORS1 is not a risk factor for late-onset psoriasis." The Journal of Investigative Dermatology **124**(1): 103-106.

Anandarajah, A. P., P. Ory, et al. (2010). "Effect of adalimumab on joint disease: features of patients with psoriatic arthritis detected by magnetic resonance imaging." Annals of the Rheumatic Diseases **69**(1): 206-209.

Anandarajah, A. P., E. M. Schwarz, et al. (2008). "The effect of etanercept on osteoclast precursor frequency and enhancing bone marrow oedema in patients with psoriatic arthritis." Annals of the Rheumatic Diseases **67**(3): 296-301.

Antoni, C., C. Dechant, et al. (2002). "Open-label study of infliximab treatment for psoriatic arthritis: Clinical and magnetic resonance imaging measurements of reduction of inflammation." Arthritis Care and Research **47**(5): 506-512.

Antoni, C., G. G. Krueger, et al. (2005a). "Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial." Annals of the Rheumatic Diseases **64**(8): 1150-1157.

Antoni, C. E., A. Kavanaugh, et al. (2005b). "Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: results from the infliximab multinational psoriatic arthritis controlled trial (IMPACT).[Erratum appears in Arthritis Rheum. 2005 Sep;52(9):2951]." Arthritis & Rheumatism **52**(4): 1227-1236.

Ash, Z., C. Gaujoux-Viala, et al. (2012a). "A systematic literature review of drug therapies for the treatment of psoriatic arthritis: current evidence and meta-analysis informing the EULAR recommendations for the management of psoriatic arthritis." Annals of the Rheumatic Diseases **71**(3): 319-326.

Ash, Z. R., I. Tinazzi, et al. (2012b). "Psoriasis patients with nail disease have a greater magnitude of underlying systemic subclinical enthesopathy than those with normal nails." Annals of the Rheumatic Diseases **71**(4): 553-556.

Augustin, M., K. Reich, et al. (2010). "Nail psoriasis in Germany: epidemiology and burden of disease." The British Journal of Dermatology **163**(3): 580-585.

Aydin, S., E. Bas, et al. (2010a). "Validation of ultrasound imaging for achilles enthesis fibrocartilage in bovines and description of changes in human with spondyloarthritis " Annals of the Rheumatic Diseases **69**(12): 2165-2168.

Aydin, S. Z., Z. Ash, et al. (2011). "Optical coherence tomography: a new tool to assess nail disease in psoriasis?" Dermatology **222**(4): 311-313.

Aydin, S. Z., Z. R. Ash, et al. (2013). "The link between enthesitis and arthritis in psoriatic arthritis: a switch to a vascular phenotype at insertions may play a role in arthritis development." Annals of the Rheumatic Diseases **72**(6): 992-995.

Aydin, S. Z., C. Castillo-Gallego, et al. (2012). "Ultrasonographic Assessment of Nail in Psoriatic Disease Shows a Link between Onychopathy and Distal Interphalangeal Joint Extensor Tendon Enthesopathy." Dermatology **225**(3): 231-235.

Aydin, S. Z., O. Karadag, et al. (2010b). "Monitoring Achilles enthesitis in ankylosing spondylitis during TNF-alpha antagonist therapy: an ultrasound study." Rheumatology **49**(3): 578-582.

Balint, P. V., D. Kane, et al. (2002). "Ultrasonography of entheseal insertions in the lower limb in spondyloarthropathy." Annals of the Rheumatic Diseases **61**(10): 905-910.

Bandinelli, F., M. Milla, et al. (2011). "Ultrasound discloses entheseal involvement in inactive and low active inflammatory bowel disease without clinical signs and symptoms of spondyloarthropathy." Rheumatology **50**(7): 1275-1279.

Baran, R. (2010). "The burden of nail psoriasis: an introduction." Dermatology **221 Suppl 1**: 1-5.

Baran, R. L. (2004). "A nail psoriasis severity index." The British Journal of Dermatology **150**(3): 568-569.

Benjamin, M. and D. McGonagle (2007a). "Histopathologic changes at "synovio-entheseal complexes" suggesting a novel mechanism for

synovitis in osteoarthritis and spondylarthritis." Arthritis & Rheumatism **56**(11): 3601-3609.

Benjamin, M. and D. McGonagle (2009). "The enthesis organ concept and its relevance to the spondyloarthropathies." Advances in experimental medicine and biology **649**: 57-70.

Benjamin, M., H. Toumi, et al. (2007b). "Microdamage and altered vascularity at the enthesis-bone interface provides an anatomic explanation for bone involvement in the HLA-B27-associated spondylarthritides and allied disorders." Arthritis & Rheumatism **56**(1): 224-233.

Bennett, A. N., D. McGonagle, et al. (2008). "Severity of baseline magnetic resonance imaging-evident sacroiliitis and HLA-B27 status in early inflammatory back pain predict radiographically evident ankylosing spondylitis at eight years." Arthritis & Rheumatism **58**(11): 3413-3418.

Bennett, A. N., A. Rehman, et al. (2009). "Evaluation of the diagnostic utility of spinal magnetic resonance imaging in axial spondylarthritis." Arthritis & Rheumatism **60**(5): 1331-1341.

Bennett, R. M. (1979). Psoriatic Arthritis. Arthritis and Related Conditions. M. DJ. Philadelphia, Lea & Febiger**:** 645.

Berth-Jones, J., J. Thompson, et al. (2008). "A study examining inter-rater and intrarater reliability of a novel instrument for assessment of psoriasis: the Copenhagen Psoriasis Severity Index." The British Journal of Dermatology **159**(2): 407-412.

Bhushan, M., T. Moore, et al. (2000). "Nailfold video capillaroscopy in psoriasis." The British Journal of Dermatology **142**(6): 1171-1176.

Blumberg, B. S., J. J. Bunim, et al. (1964). "Ara Nomenclature and Classification of Arthritis and Rheumatism (Tentative)." Arthritis & Rheumatism **7**: 93-97.

Bollow, M., T. Fischer, et al. (2000). "Quantitative analyses of sacroiliac biopsies in spondyloarthropathies: T cells and macrophages predominate in early and active sacroiliitis- cellularity correlates with the degree of enhancement detected by magnetic resonance imaging." Annals of the Rheumatic Diseases **59**(2): 135-140.

Bond, S. J., V. T. Farewell, et al. (2007). "Predictors for radiological damage in psoriatic arthritis: results from a single centre." Annals of the Rheumatic Diseases **66**(3): 370-376.

Bongartz, T., P. Harle, et al. (2005). "Successful treatment of psoriatic onycho-pachydermo periostitis (POPP) with adalimumab." Arthritis & Rheumatism **52**(1): 280-282.

Bonifati, C., F. Elia, et al. (2012). "The diagnosis of early psoriatic arthritis in an outpatient dermatological centre for psoriasis." Journal of the European Academy of Dermatology and Venereology : JEADV **26**(5): 627-633.

Bowes, J., S. Eyre, et al. (2011). "Evidence to support IL-13 as a risk locus for psoriatic arthritis but not psoriasis vulgaris." Annals of the Rheumatic Diseases **70**(6): 1016-1019.

Boyesen, P., F. M. McQueen, et al. (2011). "The OMERACT Psoriatic Arthritis Magnetic Resonance Imaging Score (PsAMRIS) is reliable and sensitive to change: results from an OMERACT workshop." The Journal of Rheumatology **38**(9): 2034-2038.

Braun, J., J. Brandt, et al. (2002). "Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial." Lancet **359**(9313): 1187-1193.

Brazzelli, V., A. Carugno, et al. (2012). "Prevalence, severity and clinical features of psoriasis in fingernails and toenails in adult patients: Italian experience." Journal of the European Academy of Dermatology and Venereology : JEADV **26**(11): 1354-1359.

Brockbank, J. E., M. Stein, et al. (2005). "Dactylitis in psoriatic arthritis: a marker for disease severity?" Annals of the Rheumatic Diseases **64**(2): 188-190.

Bronsard, V., C. Paul, et al. (2010). "What are the best outcome measures for assessing quality of life in plaque type psoriasis? A systematic review of the literature." Journal of the European Academy of Dermatology and Venereology : JEADV **24 Suppl 2**: 17-22.

Buckley, W. R. and R. L. Raleigh (1959). "Psoriasis with acro-osteolysis." New England Journal of Medicine **261**: 539-541.

Burmester, G. R., P. Hrdlicka, et al. (2008). "Adalimumab (Humira) improves the signs and symptoms of psoriatic arthritis (PsA) and is well tolerated in patients previously treated with biologics: results from a German database of PsA patients receiving Adalimumab." Annals of the Rheumatic Diseases **67**(Suppl II): 533.

Calin, A., S. Garrett, et al. (1994). "A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index." The Journal of Rheumatology **21**(12): 2281-2285.

Cannavo, S. P., F. Guarneri, et al. (2003). "Treatment of psoriatic nails with topical cyclosporin: a prospective, randomized placebo-controlled study." Dermatology **206**(2): 153-156.

Cargill, M., S. J. Schrodi, et al. (2007). "A large-scale genetic association study confirms IL12B and leads to the identification of IL23R as psoriasis-risk genes." American Journal of Human Genetics **80**(2): 273-290.

Cassell, S. E., J. D. Bieber, et al. (2007). "The modified Nail Psoriasis Severity Index: validation of an instrument to assess psoriatic nail involvement in patients with psoriatic arthritis." The Journal of Rheumatology **34**(1): 123-129.

Chandran, V., A. Gottlieb, et al. (2009). "International multicenter psoriasis and psoriatic arthritis reliability trial for the assessment of skin, joints, nails, and dactylitis." Arthritis & Rheumatism **61**(9): 1235-1242.

Chandran, V., C. T. Schentag, et al. (2007). "Sensitivity of the classification of psoriatic arthritis criteria in early psoriatic arthritis." Arthritis & Rheumatism **57**(8): 1560-1563.

Chandran, V., C. T. Schentag, et al. (2008). "Sensitivity and specificity of the CASPAR criteria for psoriatic arthritis in a family medicine clinic setting." The Journal of Rheumatology **35**(10): 2069-2070; author reply 2070.

Christophers, E., J. N. Barker, et al. (2010). "The risk of psoriatic arthritis remains constant following initial diagnosis of psoriasis among patients seen in European dermatology clinics." Journal of the European Academy of Dermatology and Venereology : JEADV **24**(5): 548-554.

Cimmino, M. A., F. Barbieri, et al. (2012). "Dynamic contrast-enhanced magnetic resonance imaging of articular and extraarticular synovial structures of the hands in patients with psoriatic arthritis." The Journal of rheumatology. Supplement **89**: 44-48.

Cimmino, M. A., M. Parodi, et al. (2005). "Dynamic magnetic resonance of the wrist in psoriatic arthritis reveals imaging patterns similar to those of rheumatoid arthritis." Arthritis Res Ther **7**(4): R725-731.

Coates, L. C., R. R. Anderson, et al. (2008a). "Clues to the pathogenesis of psoriasis and psoriatic arthritis from imaging: a literature review." The Journal of Rheumatology **35**(7): 1438-1442.

Coates, L. C., T. Aslam, et al. (2013). "Comparison of three screening tools to detect psoriatic arthritis in patients with psoriasis (CONTEST study)." British Journal of Dermatology **168**(4): 802-807.

Coates, L. C., L. S. Cawkwell, et al. (2008b). "Sustained response to long-term biologics and switching in psoriatic arthritis: results from real life experience." Annals of the Rheumatic Diseases **67**(5): 717-719.

Coates, L. C., P. G. Conaghan, et al. (2012). "Sensitivity and specificity of the classification of psoriatic arthritis criteria in early psoriatic arthritis." Arthritis & Rheumatism **64**(10): 3150-3155.

Coates, L. C., J. Fransen, et al. (2010a). "Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment." Annals of the Rheumatic Diseases **69**(1): 48-53.

Coates, L. C. and P. S. Helliwell (2010b). "Validation of minimal disease activity criteria for psoriatic arthritis using interventional trial data." Arthritis Care & Research (Hoboken) **62**(7): 965-969.

Cohen, A. D., D. Weitzman, et al. (2010). "Psoriasis and hypertension: a case-control study." Acta Dermato-Venereologica **90**(1): 23-26.

Cohen, M. R., D. J. Reda, et al. (1999). "Baseline relationships between psoriasis and psoriatic arthritis: analysis of 221 patients with active psoriatic arthritis. Department of Veterans Affairs Cooperative Study Group on Seronegative Spondyloarthropathies." The Journal of Rheumatology **26**(8): 1752-1756.

Coleman, A. J., T. J. Richardson, et al. (2013). "Histological correlates of optical coherence tomography in non-melanoma skin cancer." Skin research and technology : official journal of International Society for Bioengineering and the Skin **19**(1): 10-19.

Condon, C. and J. F. Lyons (1994). "Extensive unstable psoriasis - Morbidity and medical management." Irish Journal of Medical Science **163**(8): 381-383.

Conti, F., F. Ceccarelli, et al. (2007). "Switching tumour necrosis factor alpha antagonists in patients with ankylosing spondylitis and psoriatic arthritis: an observational study over a 5-year period." Annals of the Rheumatic Diseases **66**(10): 1393-1397.

Creamer, D., M. H. Allen, et al. (1997). "Localization of endothelial proliferation and microvascular expansion in active plaque psoriasis." The British Journal of Dermatology **136**(6): 859-865.

Cresswell, L., V. Chandran, et al. (2011). "Inflammation in an individual joint predicts damage to that joint in psoriatic arthritis." Annals of the Rheumatic Diseases **70**(2): 305-308.

D'Agostino M, A., P. Aegerter, et al. (2009). "How to evaluate and improve the reliability of power Doppler ultrasonography for assessing enthesitis in spondylarthritis." Arthritis & Rheumatism **61**(1): 61-69.

D'Agostino, M. A., P. Aegerter, et al. (2011). "How to diagnose spondyloarthritis early? Accuracy of peripheral enthesitis detection by power Doppler ultrasonography." Annals of the Rheumatic Diseases **70**(8): 1433-1440.

D'Agostino, M. A., M. Breban, et al. (2002). "Refractory inflammatory heel pain in spondylarthropathy: a significant response to infliximab documented by ultrasound." Arthritis & Rheumatism **46**(3): 840-841, author reply 841-843.

D'Agostino, M. A., R. Said-Nahal, et al. (2003). "Assessment of peripheral enthesitis in the spondylarthropathies by ultrasonography combined with power Doppler: a cross-sectional study." Arthritis & Rheumatism **48**(2): 523-533.

Dalbeth, N., K. Pui, et al. (2012). "Nail Disease in Psoriatic Arthritis: Distal Phalangeal Bone Edema Detected by Magnetic Resonance Imaging Predicts Development of Onycholysis and Hyperkeratosis." Journal of Rheumatology **39**(4): 841-843.

Dandorfer, S. W., J. Rech, et al. (2012). "Differences in the patient's and the physician's perspective of disease in psoriatic arthritis." Seminars in Arthritis & Rheumatism **42**(1): 32-41.

De Agustin, J. J., C. Moragues, et al. (2012). "A multicentre study on high-frequency ultrasound evaluation of the skin and joints in patients with psoriatic arthritis treated with infliximab." Clin Exp Rheumatol **30**(6): 879-885.

De Filippis, L. G., A. Caliri, et al. (2005). "Ultrasonography in the early diagnosis of psoriasis-associated enthesopathy." International journal of tissue reactions **27**(4): 159-162.

de Jong, E. M., B. A. Seegers, et al. (1996). "Psoriasis of the nails associated with disability in a large number of patients: results of a recent interview with 1,728 patients." Dermatology **193**(4): 300-303.

de Miguel, E., T. Cobo, et al. (2009). "Validity of enthesis ultrasound assessment in spondyloarthropathy." Annals of the Rheumatic Diseases **68**(2): 169-174.

de Miguel, E., S. Falcao, et al. (2011a). "Enthesis erosion in spondyloarthritis is not a persistent structural lesion." Annals of the Rheumatic Diseases **70**(11): 2008-2010.

de Miguel, E., S. Munoz-Fernandez, et al. (2011b). "Diagnostic accuracy of enthesis ultrasound in the diagnosis of early spondyloarthritis." Annals of the Rheumatic Diseases **70**(3): 434-439.

De Simone, C., G. Caldarola, et al. (2011). "Usefulness of ultrasound imaging in detecting psoriatic arthritis of fingers and toes in patients with psoriasis." Clinical & developmental immunology **2011**: 390726.

Delle Sedie, A., L. Riente, et al. (2010). "Ultrasound imaging for the rheumatologist XXVI. Sonographic assessment of the knee in patients with psoriatic arthritis." Clin Exp Rheumatol **28**(2): 147-152.

Delle Sedie, A., L. Riente, et al. (2011). "Ultrasound imaging for the rheumatologist. XXXII. Sonographic assessment of the foot in patients with psoriatic arthritis." Clin Exp Rheumatol **29**(2): 217-222.

Descalzo, M. A., D. Montero, et al. (2007). "Spanish registry for adverse events of biological therapy in rheumatic diseases (BIOBADASER): State report, January 26th, 2006. [Spanish]." Reumatologia Clinica **3**(1): 4-20.

Devaux, S., A. Castela, et al. (2012). "Adherence to topical treatment in psoriasis: a systematic literature review." Journal of the European Academy of Dermatology and Venereology : JEADV **26 Suppl 3**: 61-67.

Dominguez, P. L., M. E. Husni, et al. (2009). "Validity, reliability, and sensitivity-to-change properties of the psoriatic arthritis screening and evaluation questionnaire." Archives of dermatological research **301**(8): 573-579.

Dougados, M., S. van der Linden, et al. (1991). "The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy." Arthritis & Rheumatism **34**(10): 1218-1227.

Drake, L. A., D. L. Patrick, et al. (1999). "The impact of onychomycosis on quality of life: development of an international onychomycosis-specific questionnaire to measure patient quality of life." Journal of the American Academy of Dermatology **41**(2 Pt 1): 189-196.

Duffin, K. C., V. Chandran, et al. (2008). "Genetics of psoriasis and psoriatic arthritis: update and future direction." The Journal of Rheumatology **35**(7): 1449-1453.

Eastmond, C. J. and V. Wright (1979). "The nail dystrophy of psoriatic arthritis." Annals of the Rheumatic Diseases **38**(3): 226-228.

Eder, L., V. Chandran, et al. (2011a). "IL13 gene polymorphism is a marker for psoriatic arthritis among psoriasis patients." Annals of the Rheumatic Diseases **70**(9): 1594-1598.

Eder, L., T. Law, et al. (2011b). "Association between environmental factors and onset of psoriatic arthritis in patients with psoriasis." Arthritis Care & Research **63**(8): 1091-1097.

Emad, Y., Y. Ragab, et al. (2010). "Enthesitis and Related Changes in the Knees in Seronegative Spondyloarthropathies and Skin Psoriasis: Magnetic Resonance Imaging Case-Control Study." The Journal of Rheumatology **37**(8): 1709-1717.

Emad, Y., Y. Ragab, et al. (2012). "Knee Enthesitis and Synovitis on Magnetic Resonance Imaging in Patients with Psoriasis without Arthritic Symptoms." The Journal of Rheumatology **39**(10): 1979-1986.

Emad, Y., Y. Ragab, et al. (2009). "Can magnetic resonance imaging differentiate undifferentiated arthritis based on knee imaging?" The Journal of Rheumatology **36**(9): 1963-1970.

Emery, P., T. K. Kvien, et al. (2012). "Combination etanercept and methotrexate provides better disease control in very early (<=4 months) versus early rheumatoid arthritis (>4 months and <2 years): post hoc analyses from the COMET study." Annals of the Rheumatic Diseases **71**(6): 989-992.

Erdem, C. Z., N. S. Tekin, et al. (2008). "MR imaging features of foot involvement in patients with psoriasis." European Journal of Radiology **67**(3): 521-525.

Fagerli, K. M., E. Lie, et al. (2013). "The role of methotrexate co-medication in TNF-inhibitor treatment in patients with psoriatic arthritis: results from 440 patients included in the NOR-DMARD study." Annals of the Rheumatic Diseases.

Falsetti, P., B. Frediani, et al. (2002). "Enthesitis of proximal insertion of the deltoid in the course of seronegative spondyloarthritis. An atypical enthesitis that can mime impingement syndrome." Scandinavian Journal of Rheumatology **31**(3): 158-162.

Falsetti, P., B. Frediani, et al. (2003). "Sonographic study of calcaneal entheses in erosive osteoarthritis, nodal osteoarthritis, rheumatoid arthritis and psoriatic arthritis." Scandinavian Journal of Rheumatology **32**(4): 229-234.

Fan, X., S. Yang, et al. (2007). "Comparison of clinical features of HLA-Cw*0602-positive and -negative psoriasis patients in a Han Chinese population." Acta Dermato-Venereologica **87**(4): 335-340.

Farouk, H. M., A. A. Mostafa, et al. (2010). "Value of entheseal ultrasonography and serum cartilage oligomeric matrix protein in the preclinical diagnosis of psoriatic arthritis." Clinical medicine insights. Arthritis and musculoskeletal disorders **3**: 7-14.

Fearon, U., K. Griosios, et al. (2003). "Angiopoietins, growth factors, and vascular morphology in early arthritis." The Journal of Rheumatology **30**(2): 260-268.

Feliciani, C., A. Zampetti, et al. (2004). "Nail psoriasis: combined therapy with systemic cyclosporin and topical calcipotriol." Journal of Cutaneous Medicine and Surgery **8**(2): 122-125.

Fernandez-Penas, P., M. Jones-Caballero, et al. (2012). "Comparison of Skindex-29, Dermatology Life Quality Index, Psoriasis Disability Index and Medical Outcome Study Short Form 36 in patients with mild to severe psoriasis." The British Journal of Dermatology **166**(4): 884-887.

Feydy, A., M. C. Lavie-Brion, et al. (2012). "Comparative study of MRI and power Doppler ultrasonography of the heel in patients with spondyloarthritis with and without heel pain and in controls." Annals of the Rheumatic Diseases **71**(4): 498-503.

Filer, C., P. Ho, et al. (2008). "Investigation of association of the IL12B and IL23R genes with psoriatic arthritis." Arthritis & Rheumatism **58**(12): 3705-3709.

Filippucci, E., S. Z. Aydin, et al. (2009). "Reliability of high-resolution ultrasonography in the assessment of Achilles tendon enthesopathy in seronegative spondyloarthropathies." Annals of the Rheumatic Diseases **68**(12): 1850-1855.

Finlay, A. Y. and S. E. Kelly (1987). "Psoriasis--an index of disability." Clinical and Experimental Dermatology **12**(1): 8-11.

Finlay, A. Y. and G. K. Khan (1994). "Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use." Clinical and Experimental Dermatology **19**(3): 210-216.

Fiocco, U., L. Cozzi, et al. (1996). "Long-term sonographic follow-up of rheumatoid and psoriatic proliferative knee joint synovitis." British Journal of Rheumatology **35**(2): 155-163.

Fiocco, U., F. Ferro, et al. (2005). "Rheumatoid and psoriatic knee synovitis: clinical, grey scale, and power Doppler ultrasound assessment of the

response to etanercept." Annals of the Rheumatic Diseases **64**(6): 899-905.

Fournié, B., L. Crognier, et al. (1999). "Proposed classification criteria of psoriatic arthritis. A preliminary study in 260 patients." Revue du rhumatisme **66**(10): 446-456.

Fournié, B., N. Margarit-Coll, et al. (2006). "Extrasynovial ultrasound abnormalities in the psoriatic finger. Prospective comparative power-doppler study versus rheumatoid arthritis." Joint, Bone, Spine : Revue du Rhumatisme **73**(5): 527-531.

Fransen, J., C. Antoni, et al. (2006). "Performance of response criteria for assessing peripheral arthritis in patients with psoriatic arthritis: analysis of data from randomised controlled trials of two tumour necrosis factor inhibitors." Annals of the Rheumatic Diseases **65**(10): 1373-1378.

Frediani, B., P. Falsetti, et al. (2001). "Quadricepital tendon enthesitis in psoriatic arthritis and rheumatoid arthritis: ultrasound examinations and clinical correlations." The Journal of Rheumatology **28**(11): 2566-2568.

Fredriksson, T. and U. Pettersson (1978). "Severe psoriasis--oral therapy with a new retinoid." Dermatologica **157**(4): 238-244.

Freeston, J. E., L. C. Coates, et al. (2012). "Is there subclinical enthesitis in early psoriatic arthritis? A clinical comparison with power doppler ultrasound." Arthritis Care & Research **64**(10): 1617-1621.

Fry, L. (1988). "Psoriasis." The British Journal of Dermatology **119**(4): 445-461.

Gaffney, K., J. Cookson, et al. (1995). "Quantification of rheumatoid synovitis by magnetic resonance imaging." Arthritis & Rheumatism **38**(11): 1610-1617.

Garg, A., D. D. Gladman, et al. (2012). "The need to define musculoskeletal inflammation: a report from the GRAPPA 2010 annual meeting." The Journal of Rheumatology **39**(2): 413-414.

Garrett, S., T. Jenkinson, et al. (1994). "A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index." Journal of Rheumatology **21**(12): 2286-2291.

Geitzenauer, W., C. K. Hitzenberger, et al. (2011). "Retinal optical coherence tomography: past, present and future perspectives." The British Journal of Ophthalmology **95**(2): 171-177.

Gelfand, J. M., D. D. Gladman, et al. (2005a). "Epidemiology of psoriatic arthritis in the population of the United States." Journal of the American Academy of Dermatology **53**(4): 573.

Gelfand, J. M., R. Weinstein, et al. (2005b). "Prevalence and treatment of psoriasis in the United Kingdom: a population-based study." Archives of dermatology **141**(12): 1537-1541.

Genc, H., B. Duyur Cakit, et al. (2007). "The effects of sulfasalazine treatment on enthesal abnormalities of inflammatory rheumatic diseases." Clin Rheumatol **26**(7): 1104-1110.

Genovese, M. C., P. J. Mease, et al. (2007). "Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy.[Erratum appears in J Rheumatol. 2007 Jun;34(6):1439]." Journal of Rheumatology **34**(5): 1040-1050.

Ghanem, N., M. Uhl, et al. (2007). "MRI in psoriatic arthritis with hand and foot involvement." Rheumatology International **27**(4): 387-393.
Gisondi, P., L. Idolazzi, et al. (2012). "Ultrasonography reveals nail thickening in patients with chronic plaque psoriasis." Archives of dermatological research **304**(9): 727-732.
Gisondi, P., I. Tinazzi, et al. (2008). "Lower limb enthesopathy in patients with psoriasis without clinical signs of arthropathy: a hospital-based case-control study." Annals of the Rheumatic Diseases **67**(1): 26-30.
Gladman, D. D., R. J. Cook, et al. (2004). "The clinical assessment of patients with psoriatic arthritis: results of a reliability study of the spondyloarthritis research consortium of Canada." The Journal of Rheumatology **31**(6): 1126-1131.
Gladman, D. D. and V. T. Farewell (1999). "Progression in psoriatic arthritis: role of time varying clinical indicators." The Journal of Rheumatology **26**(11): 2409-2413.
Gladman, D. D., V. T. Farewell, et al. (1995). "Clinical indicators of progression in psoriatic arthritis: multivariate relative risk model." The Journal of Rheumatology **22**(4): 675-679.
Gladman, D. D., R. D. Inman, et al. (2007a). "International spondyloarthritis interobserver reliability exercise--the INSPIRE study: II. Assessment of peripheral joints, enthesitis, and dactylitis." The Journal of Rheumatology **34**(8): 1740-1745.
Gladman, D. D., P. J. Mease, et al. (2010). "Risk factors for radiographic progression in psoriatic arthritis: subanalysis of the randomized controlled trial ADEPT." Arthritis Res Ther **12**(3): R113.
Gladman, D. D., P. J. Mease, et al. (2007b). "Adalimumab for long-term treatment of psoriatic arthritis: forty-eight week data from the adalimumab effectiveness in psoriatic arthritis trial." Arthritis & Rheumatism **56**(2): 476-488.
Gladman, D. D., C. T. Schentag, et al. (2009). "Development and initial validation of a screening questionnaire for psoriatic arthritis: the Toronto Psoriatic Arthritis Screen (ToPAS)." Annals of the Rheumatic Diseases **68**(4): 497-501.
Gladman, D. D., R. Shuckett, et al. (1987a). "Psoriatic arthritis (PsA)--an analysis of 220 patients." The Quarterly Journal of Medicine **62**(238): 127-141.
Gladman, D. D., R. Shuckett, et al. (1987b). "Psoriatic arthritis (PSA)--an analysis of 220 patients." Q J Med **62**(238): 127-141.
Gladman, D. D., F. Stafford-Brady, et al. (1990). "Longitudinal study of clinical and radiological progression in psoriatic arthritis." The Journal of Rheumatology **17**(6): 809-812.
Gomez-Reino, J. J., L. Carmona, et al. (2006). "Switching TNF antagonists in patients with chronic arthritis: an observational study of 488 patients over a four-year period." Arthritis Res Ther **8**(1): R29.
Gossec, L., J. S. Smolen, et al. (2012). "European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies." Annals of the Rheumatic Diseases **71**(1): 4-12.
Gottlieb, A., A. Mendelsohn, et al. (2008). "Ustekinumab, a human interleukin -12/23 monoclonal antibody, significantly improves overall skin response and health related quality of life in patients with

psoriatic arthritis." Annals of the Rheumatic Diseases **67**(Suppl II): 526.
Gottlieb, A., A. Menter, et al. (2009). "Ustekinumab, a human interleukin 12/23 monoclonal antibody, for psoriatic arthritis: randomised, double-blind, placebo-controlled, crossover trial.[Erratum appears in Lancet. 2009 Apr 18;373(9672):1340]." Lancet **373**(9664): 633-640.
Green, F. A. (1968). "Distal interphalangeal joint disease and nail abnormalities." Annals of the Rheumatic Diseases **27**(1): 55-59.
Gudjonsson, J. E. and J. T. Elder (2007). "Psoriasis: epidemiology." Clinics in dermatology **25**(6): 535-546.
Gudjonsson, J. E., A. Karason, et al. (2002). "HLA-Cw6-positive and HLA-Cw6-negative patients with Psoriasis vulgaris have distinct clinical features." The Journal of Investigative Dermatology **118**(2): 362-365.
Gudjonsson, J. E., A. Karason, et al. (2006). "Distinct clinical differences between HLA-Cw*0602 positive and negative psoriasis patients--an analysis of 1019 HLA-C- and HLA-B-typed patients." The Journal of Investigative Dermatology **126**(4): 740-745.
Guero, S., S. Guichard, et al. (1994). "Ligamentary structure of the base of the nail." Surgical and Radiologic Anatomy : SRA **16**(1): 47-52.
Gumusel, M., M. Ozdemir, et al. (2011). "Evaluation of the efficacy of methotrexate and cyclosporine therapies on psoriatic nails: a one-blind, randomized study." Journal of the European Academy of Dermatology and Venereology : JEADV **25**(9): 1080-1084.
Gutierrez, M., L. Di Geso, et al. (2012). "Development of a preliminary US power Doppler composite score for monitoring treatment in PsA." Rheumatology **51**(7): 1261-1268.
Gutierrez, M., E. Filippucci, et al. (2010). "A sonographic spectrum of psoriatic arthritis: "the five targets"." Clin Rheumatol **29**(2): 133-142.
Gutierrez, M., E. Filippucci, et al. (2011a). "Subclinical entheseal involvement in patients with psoriasis: an ultrasound study." Seminars in Arthritis & Rheumatism **40**(5): 407-412.
Gutierrez, M., E. Filippucci, et al. (2011b). "Differential diagnosis between rheumatoid arthritis and psoriatic arthritis: the value of ultrasound findings at metacarpophalangeal joints level." Annals of the Rheumatic Diseases **70**(6): 1111-1114.
Gutierrez, M., X. Wortsman, et al. (2009). "High-frequency sonography in the evaluation of psoriasis: nail and skin involvement." Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine **28**(11): 1569-1574.
Gutierrez, M., M. Zeiler, et al. (2011c). "Sonographic subclinical entheseal involvement in dialysis patients." Clin Rheumatol **30**(7): 907-913.
Hamdi, W., M. Chelli-Bouaziz, et al. (2011). "Correlations among clinical, radiographic, and sonographic scores for enthesitis in ankylosing spondylitis." Joint, Bone, Spine : Revue du Rhumatisme **78**(3): 270-274.
Hammer, H. B. and T. K. Kvien (2011). "Ultrasonography shows significant improvement in wrist and ankle tenosynovitis in rheumatoid arthritis patients treated with adalimumab." Scandinavian Journal of Rheumatology **40**(3): 178-182.
Han, C., J. H. Lofland, et al. (2011). "Increased prevalence of psychiatric disorders and health care-associated costs among patients with

moderate-to-severe psoriasis." Journal of Drugs in Dermatology : JDD **10**(8): 843-850.

Handfield-Jones, S. E., J. Boyle, et al. (1987). "Local PUVA treatment for nail psoriasis." The British Journal of Dermatology **116**(2): 280-281.

Haroon, M. and O. Fitzgerald (2012). "Pathogenetic overview of psoriatic disease." The Journal of rheumatology. Supplement **89**: 7-10.

Haroon, M., B. Kirby, et al. (2013). "High prevalence of psoriatic arthritis in patients with severe psoriasis with suboptimal performance of screening questionnaires." Annals of the Rheumatic Diseases **72**(5): 736-740.

Healy, P. J., C. Groves, et al. (2008a). "MRI changes in psoriatic dactylitis--extent of pathology, relationship to tenderness and correlation with clinical indices." Rheumatology **47**(1): 92-95.

Healy, P. J. and P. S. Helliwell (2007). "Measuring dactylitis in clinical trials: which is the best instrument to use?" The Journal of Rheumatology **34**(6): 1302-1306.

Healy, P. J. and P. S. Helliwell (2008b). "Measuring clinical enthesitis in psoriatic arthritis: assessment of existing measures and development of an instrument specific to psoriatic arthritis." Arthritis & Rheumatism **59**(5): 686-691.

Heiberg, M. S., C. Kaufmann, et al. (2007). "The comparative effectiveness of anti-TNF therapy and methotrexate in patients with psoriatic arthritis: 6 month results from a longitudinal, observational, multicentre study." Annals of the Rheumatic Diseases **66**(8): 1038-1042.

Heiberg, M. S., W. Koldingsnes, et al. (2008). "The comparative one-year performance of anti-tumor necrosis factor alpha drugs in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: results from a longitudinal, observational, multicenter study." Arthritis & Rheumatism **59**(2): 234-240.

Helliwell, P., A. Marchesoni, et al. (1991). "A re-evaluation of the osteoarticular manifestations of psoriasis." British Journal of Rheumatology **30**(5): 339-345.

Helliwell, P. S. (2009). "Established psoriatic arthritis: clinical aspects." The Journal of rheumatology. Supplement **83**: 21-23.

Helliwell, P. S., J. Firth, et al. (2005). "Development of an assessment tool for dactylitis in patients with psoriatic arthritis." The Journal of Rheumatology **32**(9): 1745-1750.

Helliwell, P. S. and G. Porter (2007). "Sensitivity and specificity of plain radiographic features of peripheral enthesopathy at major sites in psoriatic arthritis." Skeletal Radiology **36**(11): 1061-1066.

Hern, S. and P. S. Mortimer (2007). "In vivo quantification of microvessels in clinically uninvolved psoriatic skin and in normal skin." The British Journal of Dermatology **156**(6): 1224-1229.

Herron, M. D., M. Hinckley, et al. (2005). "Impact of obesity and smoking on psoriasis presentation and management." Archives of dermatology **141**(12): 1527-1534.

Heuft-Dorenbosch, L., A. Spoorenberg, et al. (2003). "Assessment of enthesitis in ankylosing spondylitis." Annals of the Rheumatic Diseases **62**(2): 127-132.

Ho, P. Y., A. Barton, et al. (2008). "Investigating the role of the HLA-Cw*06 and HLA-DRB1 genes in susceptibility to psoriatic arthritis: comparison with psoriasis and undifferentiated inflammatory arthritis." Annals of the Rheumatic Diseases **67**(5): 677-682.

Ho, P. Y., A. Barton, et al. (2007). "HLA-Cw6 and HLA-DRB1*07 together are associated with less severe joint disease in psoriatic arthritis." Annals of the Rheumatic Diseases **66**(6): 807-811.

Hodgson, R. J., N. Menon, et al. (2012). "Quantitative MRI measurements of the Achilles tendon in spondyloarthritis using ultrashort echo times." The British journal of radiology **85**(1015): e293-299.

Hossler, E. W., M. S. Maroon, et al. (2011). "Gastric bypass surgery improves psoriasis." Journal of the American Academy of Dermatology **65**(1): 198-200.

Huang, Y. H., L. C. Yang, et al. (2010). "Relationships between obesity and the clinical severity of psoriasis in Taiwan." Journal of the European Academy of Dermatology and Venereology : JEADV **24**(9): 1035-1039.

Husein El-Ahmed, H., F. Garrido-Pareja, et al. (2012). "Vessel resistance to blood flow in the nailfold in patients with psoriasis: a prospective case-control echo Doppler-based study." British Journal of Dermatology **166**(1): 54-58.

Husni, M. E., K. H. Meyer, et al. (2007). "The PASE questionnaire: Pilot-testing a Psoriatic Arthritis Screening and Evaluation tool." Journal of the American Academy of Dermatology **57**(4): 581-587.

Iagnocco, A., L. Riente, et al. (2009). "Ultrasound imaging for the rheumatologist. XXII. Achilles tendon involvement in spondyloarthritis. A multi-centre study using high frequency volumetric probe." Clinical & Experimental Rheumatology **27**(4): 547-551.

Iagnocco, A., A. Spadaro, et al. (2012). "Power Doppler ultrasonographic evaluation of enthesitis in psoriatic arthritis. A multi-center study." Joint, Bone, Spine : Revue du Rhumatisme **79**(3): 324-325.

Ibrahim, G., C. Groves, et al. (2010). "Ultrasound examination of the Leeds Enthesitis Index in psoriatic arthritis." Revista Latinoamericana de Psoriasis y Artritis Psoriasica **1**: 1-14.

Ibrahim, G. H., M. H. Buch, et al. (2009). "Evaluation of an existing screening tool for psoriatic arthritis in people with psoriasis and the development of a new instrument: the Psoriasis Epidemiology Screening Tool (PEST) questionnaire." Clinical & Experimental Rheumatology **27**(3): 469-474.

Ichikawa, N., A. Taniguchi, et al. (2012). "Performance of hands and feet radiographs in differentiation of psoriatic arthritis from rheumatoid arthritis." International journal of rheumatic diseases **15**(5): 462-467.

Igarashi, A., T. Kato, et al. (2012). "Efficacy and safety of ustekinumab in Japanese patients with moderate-to-severe plaque-type psoriasis: Long-term results from a phase 2/3 clinical trial." The Journal of Dermatology **39**(3): 242-252.

Jenkinson, T. R., P. A. Mallorie, et al. (1994). "Defining spinal mobility in ankylosing spondylitis (AS). The Bath AS Metrology Index." The Journal of Rheumatology **21**(9): 1694-1698.

Jevtic, V., I. Watt, et al. (1995). "Distinctive radiological features of small hand joints in rheumatoid arthritis and seronegative spondyloarthritis

demonstrated by contrast-enhanced (Gd-DTPA) magnetic resonance imaging." Skeletal Radiology **24**(5): 351-355.

Jiaravuthisan, M. M., D. Sasseville, et al. (2007). "Psoriasis of the nail: anatomy, pathology, clinical presentation, and a review of the literature on therapy." Journal of the American Academy of Dermatology **57**(1): 1-27.

Jones, S. M., J. B. Armas, et al. (1994). "Psoriatic arthritis: outcome of disease subsets and relationship of joint disease to nail and skin disease." British Journal of Rheumatology **33**(9): 834-839.

Kammer, G. M., N. A. Soter, et al. (1979). "Psoriatic arthritis: a clinical, immunologic and HLA study of 100 patients." Seminars in Arthritis & Rheumatism **9**(2): 75-97.

Kane, D., T. Greaney, et al. (1999). "Ultrasonography in the diagnosis and management of psoriatic dactylitis." The Journal of Rheumatology **26**(8): 1746-1751.

Kane, D., L. Stafford, et al. (2003). "A prospective, clinical and radiological study of early psoriatic arthritis: an early synovitis clinic experience." Rheumatology **42**(12): 1460-1468.

Kavanaugh, A., C. E. Antoni, et al. (2006). "The Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT): results of radiographic analyses after 1 year." Annals of the Rheumatic Diseases **65**(8): 1038-1043.

Kavanaugh, A., I. McInnes, et al. (2009). "Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four-week efficacy and safety results of a randomized, placebo-controlled study." Arthritis & Rheumatism **60**(4): 976-986.

Kavanaugh, A., P. Mease, et al. (2008). "Golimumab, a new, human, TNF alpha antibody administered subcutaneously every 4 weeks in psoriatic arthritis patients: 52 week efficacy and safety results of the randomised, placebo-controlled Go-Reveal study, EULAR abstract." Annals of the Rheumatic Diseases **67**(Suppl II): 99.

Kavanaugh, A., D. van der Heijde, et al. (2012a). "Golimumab in psoriatic arthritis: one-year clinical efficacy, radiographic, and safety results from a phase III, randomized, placebo-controlled trial " Arthritis & Rheumatism **64**(8): 2504-2517.

Kavanaugh, A., D. van der Heijde, et al. (2012b). "Golimumab in psoriatic arthritis: one-year clinical efficacy, radiographic, and safety results from a phase III, randomized, placebo-controlled trial." Arthritis & Rheumatism **64**(8): 2504-2517.

Kellgren, J. H. and J. S. Lawrence (1957). "Radiological assessment of osteo-arthrosis." Annals of the Rheumatic Diseases **16**(4): 494-502.

Khan, M., C. Schentag, et al. (2003). "Clinical and radiological changes during psoriatic arthritis disease progression." The Journal of Rheumatology **30**(5): 1022-1026.

Khraishi, M., E. Chouela, et al. (2012). "High prevalence of psoriatic arthritis in a cohort of patients with psoriasis seen in a dermatology practice." Journal of Cutaneous Medicine and Surgery **16**(2): 122-127.

Kiris, A., A. Kaya, et al. (2006). "Assessment of enthesitis in ankylosing spondylitis by power Doppler ultrasonography." Skeletal Radiology **35**(7): 522-528.

Kiuru, M. J., M. Niva, et al. (2005). "Bone stress injuries in asymptomatic elite recruits: a clinical and magnetic resonance imaging study." The American Journal of Sports Medicine **33**(2): 272-276.

Konig, H., J. Sieper, et al. (1990). "Rheumatoid arthritis: evaluation of hypervascular and fibrous pannus with dynamic MR imaging enhanced with Gd-DTPA." Radiology **176**(2): 473-477.

Korendowych, E., P. Owen, et al. (2005). "The clinical and genetic associations of anti-cyclic citrullinated peptide antibodies in psoriatic arthritis." Rheumatology **44**(8): 1056-1060.

Korver, J. E., A. M. Langewouters, et al. (2006). "Therapeutic effects of a 12-week course of alefacept on nail psoriasis." Journal of the European Academy of Dermatology and Venereology : JEADV **20**(10): 1252-1255.

Kristensen, L. E., P. Geborek, et al. (2009). "Dose escalation of infliximab therapy in arthritis patients is related to diagnosis and concomitant methotrexate treatment: Observational results from the South Swedish Arthritis Treatment Group register." Rheumatology **48**(3): 243-245.

Kristensen, L. E., A. Gulfe, et al. (2008). "Efficacy and tolerability of anti-tumour necrosis factor therapy in psoriatic arthritis patients: results from the South Swedish Arthritis Treatment Group register." Annals of the Rheumatic Diseases **67**(3): 364-369.

Krueger, G. G., S. R. Feldman, et al. (2000). "Two considerations for patients with psoriasis and their clinicians: what defines mild, moderate, and severe psoriasis? What constitutes a clinically significant improvement when treating psoriasis?" Journal of the American Academy of Dermatology **43**(2 Pt 1): 281-285.

Kurd, S. K., A. B. Troxel, et al. (2010). "The risk of depression, anxiety, and suicidality in patients with psoriasis: a population-based cohort study." Archives of dermatology **146**(8): 891-895.

Kurosaka, D., K. Hirai, et al. (2010). "Clinical significance of serum levels of vascular endothelial growth factor, angiopoietin-1, and angiopoietin-2 in patients with rheumatoid arthritis." The Journal of Rheumatology **37**(6): 1121-1128.

Kvamme, M. K., E. Lie, et al. (2012). "Two-year direct and indirect costs for patients with inflammatory rheumatic joint diseases: data from real-life follow-up of patients in the NOR-DMARD registry." Rheumatology **51**(9): 1618-1627.

Langley, R. G. and C. N. Ellis (2004). "Evaluating psoriasis with Psoriasis Area and Severity Index, Psoriasis Global Assessment, and Lattice System Physician's Global Assessment." Journal of the American Academy of Dermatology **51**(4): 563-569.

Laurent, M. R. (1985). "Psoriatic arthritis." Clinics in rheumatic diseases **11**(1): 61-85.

Lehtinen, A., M. Leirisalo-Repo, et al. (1995). "Persistence of enthesopathic changes in patients with spondylarthropathy during a 6-month follow-up." Clinical & Experimental Rheumatology **13**(6): 733-736.

Lehtinen, A., M. Taavitsainen, et al. (1994). "Sonographic analysis of enthesopathy in the lower extremities of patients with spondylarthropathy." Clinical & Experimental Rheumatology **12**(2): 143-148.

Leung, Y. Y., L. S. Tam, et al. (2010). "Evaluation of the CASPAR criteria for psoriatic arthritis in the Chinese population." Rheumatology **49**(1): 112-115.

Leung, Y. Y., L. S. Tam, et al. (2008). "Comparison of 4 functional indexes in psoriatic arthritis with axial or peripheral disease subgroups using Rasch analyses." The Journal of Rheumatology **35**(8): 1613-1621.

Levy, A. R., A. M. Davie, et al. (2012). "Economic burden of moderate to severe plaque psoriasis in Canada." International Journal of Dermatology **51**(12): 1432-1440.

Lin, T. Y., L. C. See, et al. (2011). "Quality of life in patients with psoriasis in northern Taiwan." Chang Gung medical journal **34**(2): 186-196.

Liu, Y., C. Helms, et al. (2008). "A genome-wide association study of psoriasis and psoriatic arthritis identifies new disease loci." Public Library of Science: Genetics **4**(3): e1000041.

Long, C. C., A. Y. Finlay, et al. (1992). "The rule of hand: 4 hand areas = 2 FTU = 1 g." Archives of dermatology **128**(8): 1129-1130.

Love, T. J., B. Gudbjornsson, et al. (2007). "Psoriatic arthritis in Reykjavik, Iceland: prevalence, demographics, and disease course." The Journal of Rheumatology **34**(10): 2082-2088.

Love, T. J., A. A. Qureshi, et al. (2011). "Prevalence of the Metabolic Syndrome in Psoriasis: Results From the National Health and Nutrition Examination Survey, 2003-2006." Archives of dermatology **147**(4): 419-424.

Lubrano, E., A. Marchesoni, et al. (2009a). "Psoriatic arthritis spondylitis radiology index: a modified index for radiologic assessment of axial involvement in psoriatic arthritis." The Journal of Rheumatology **36**(5): 1006-1011.

Lubrano, E., A. Marchesoni, et al. (2009b). "The radiological assessment of axial involvement in psoriatic arthritis: a validation study of the BASRI total and the modified SASSS scoring methods." Clinical & Experimental Rheumatology **27**(6): 977-980.

Lubrano, E., R. Scrivo, et al. (2012). "Is the nail psoriasis severity index reliable in the assessment of nail psoriasis by rheumatologists?" Arthritis Care & Research **64**(3): 455-458.

Luger, T. A., J. Barker, et al. (2009). "Sustained improvement in joint pain and nail symptoms with etanercept therapy in patients with moderate-to-severe psoriasis." Journal of the European Academy of Dermatology and Venereology : JEADV **23**(8): 896-904.

Ly, J., C. Pinto, et al. (2009). "Axial bone proliferation causing cervical myelopathy in the mutilans form of psoriatic arthritis despite peripheral bone erosion." Annals of the Rheumatic Diseases **68**(3): 443-444.

Maejima, H., T. Taniguchi, et al. (2010). "Evaluation of nail disease in psoriatic arthritis by using a modified nail psoriasis severity score index." International Journal of Dermatology **49**(8): 901-906.

Magin, P., J. Adams, et al. (2009). "The psychological sequelae of psoriasis: results of a qualitative study." Psychology, health & medicine **14**(2): 150-161.

Magin, P., G. Heading, et al. (2010). "Sex and the skin: a qualitative study of patients with acne, psoriasis and atopic eczema." Psychology, health & medicine **15**(4): 454-462.

Mahrle, G., H. J. Schulze, et al. (1995). "Low-dose short-term cyclosporine versus etretinate in psoriasis: improvement of skin, nail, and joint involvement." Journal of the American Academy of Dermatology **32**(1): 78-88.

Maksymowych, W. P., C. Mallon, et al. (2009). "Development and validation of the Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index." Annals of the Rheumatic Diseases **68**(6): 948-953.

Mander, M., J. M. Simpson, et al. (1987). "Studies with an enthesis index as a method of clinical assessment in ankylosing spondylitis." Annals of the Rheumatic Diseases **46**(3): 197-202.

Manger, B., H. M. Lorenz, et al. (2008). "Adalimumab (Humira) improves the signs and symptoms of joint, skin and nail manifestations of psoriatic arthritis (PsA): results from a German database of PsA patients receiving adalimumab." Annals of the Rheumatic Diseases **67**(Suppl II): 528.

Marchesoni, A., O. De Lucia, et al. (2012). "Entheseal power Doppler ultrasonography: a comparison of psoriatic arthritis and fibromyalgia." The Journal of rheumatology. Supplement **89**: 29-31.

Marsal, S., L. Armadans-Gil, et al. (1999). "Clinical, radiographic and HLA associations as markers for different patterns of psoriatic arthritis." Rheumatology **38**(4): 332-337.

Marx, J. L. and R. K. Scher (1980). "Response of psoriatic nails to oral photochemotherapy." Archives of dermatology **116**(9): 1023-1024.

Marzo-Ortega, H., D. McGonagle, et al. (2005). "Infliximab in combination with methotrexate in active ankylosing spondylitis: a clinical and imaging study." Annals of the Rheumatic Diseases **64**(11): 1568-1575.

Marzo-Ortega, H., D. McGonagle, et al. (2007a). "Efficacy of infliximab on MRI-determined bone oedema in psoriatic arthritis." Annals of the Rheumatic Diseases **66**(6): 778-781.

Marzo-Ortega, H., P. O'Connor, et al. (2007b). "Sacroiliac joint biopsies in early sacroiliitis." Rheumatology **46**(7): 1210-1211.

Marzo-Ortega, H., S. F. Tanner, et al. (2009). "Magnetic resonance imaging in the assessment of metacarpophalangeal joint disease in early psoriatic and rheumatoid arthritis." Scandinavian Journal of Rheumatology **38**(2): 79-83.

Mazzotta, A., M. Esposito, et al. (2009). "Efficacy and safety of etanercept in psoriasis after switching from other treatments: an observational study." American Journal of Clinical Dermatology **10**(5): 319-324.

Mazzotti, E., A. Picardi, et al. (2003). "Sensitivity of the Dermatology Life Quality Index to clinical change in patients with psoriasis." The British Journal of Dermatology **149**(2): 318-322.

McGonagle, D. (2009). "Enthesitis: an autoinflammatory lesion linking nail and joint involvement in psoriatic disease." Journal of the European Academy of Dermatology & Venereology **23 Suppl 1**: 9-13.

McGonagle, D., Z. Ash, et al. (2011a). "The early phase of psoriatic arthritis." Annals of the Rheumatic Diseases **70 Suppl 1**: i71-76.

McGonagle, D., Z. R. Ash, et al. (2011b). "MRI for the assessment and monitoring of RA--what can it tell us?" Nature reviews. Rheumatology **7**(3): 185-189.

McGonagle, D., P. G. Conaghan, et al. (1999). "Psoriatic arthritis: a unified concept twenty years on." Arthritis & Rheumatism **42**(6): 1080-1086.

McGonagle, D. and P. Emery (2000). "Enthesitis, osteitis, microbes, biomechanics, and immune reactivity in ankylosing spondylitis." The Journal of Rheumatology **27**(10): 2302-2304.

McGonagle, D., W. Gibbon, et al. (1998a). "Classification of inflammatory arthritis by enthesitis." Lancet **352**(9134): 1137-1140.

McGonagle, D., W. Gibbon, et al. (1998b). "Characteristic magnetic resonance imaging entheseal changes of knee synovitis in spondylarthropathy." Arthritis & Rheumatism **41**(4): 694-700.

McGonagle, D., H. Marzo-Ortega, et al. (2002). "The role of biomechanical factors and HLA-B27 in magnetic resonance imaging-determined bone changes in plantar fascia enthesopathy." Arthritis & Rheumatism **46**(2): 489-493.

McGonagle, D., A. L. Tan, et al. (2009a). "The nail as a musculoskeletal appendage--implications for an improved understanding of the link between psoriasis and arthritis." Dermatology **218**(2): 97-102.

McGonagle, D., A. L. Tan, et al. (2009b). "Microanatomic studies to define predictive factors for the topography of periarticular erosion formation in inflammatory arthritis." Arthritis & Rheumatism **60**(4): 1042-1051.

McGonagle, D., R. J. Wakefield, et al. (2008). "Distinct topography of erosion and new bone formation in achilles tendon enthesitis: implications for understanding the link between inflammation and bone formation in spondylarthritis." Arthritis & Rheumatism **58**(9): 2694-2699.

McHugh, N. J., C. Balachrishnan, et al. (2003). "Progression of peripheral joint disease in psoriatic arthritis: a 5-yr prospective study." Rheumatology **42**(6): 778-783.

McQueen, F., M. Lassere, et al. (2007). "Developing a magnetic resonance imaging scoring system for peripheral psoriatic arthritis." The Journal of Rheumatology **34**(4): 859-861.

McQueen, F., M. Lassere, et al. (2009). "Testing an OMERACT MRI scoring system for peripheral psoriatic arthritis in cross-sectional and longitudinal settings." The Journal of Rheumatology **36**(8): 1811-1815.

McQueen, F., R. Lloyd, et al. (2011). "Zoledronic acid does not reduce MRI erosive progression in PsA but may suppress bone oedema: the Zoledronic Acid in Psoriatic Arthritis (ZAPA) Study." Annals of the Rheumatic Diseases **70**(6): 1091-1094.

Mease, P., M. C. Genovese, et al. (2011). "Abatacept in the treatment of patients with psoriatic arthritis: results of a six-month, multicenter, randomized, double-blind, placebo-controlled, phase II trial." Arthritis & Rheumatism **63**(4): 939-948.

Mease, P. J., D. D. Gladman, et al. (2006a). "Alefacept in combination with methotrexate for the treatment of psoriatic arthritis: results of a randomized, double-blind, placebo-controlled study." Arthritis & Rheumatism **54**(5): 1638-1645.

Mease, P. J., D. D. Gladman, et al. (2005). "Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial." Arthritis & Rheumatism **52**(10): 3279-3289.

Mease, P. J., B. S. Goffe, et al. (2000). "Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial." Lancet **356**(9227): 385-390.

Mease, P. J., A. J. Kivitz, et al. (2006b). "Continued inhibition of radiographic progression in patients with psoriatic arthritis following 2 years of treatment with etanercept." Journal of Rheumatology **33**(4): 712-721.

Mease, P. J., A. J. Kivitz, et al. (2004). "Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression." Arthritis & Rheumatism **50**(7): 2264-2272.

Mease, P. J., K. Reich, et al. (2009). "Alefacept with methotrexate for treatment of psoriatic arthritis: open-label extension of a randomized, double-blind, placebo-controlled study.[Erratum appears in J Am Acad Dermatol. 2009 Sep;61(3):507]." Journal of the American Academy of Dermatology **60**(3): 402-411.

Mehta, N. N., Y. Yu, et al. (2011). "Systemic and vascular inflammation in patients with moderate to severe psoriasis as measured by [18F]-fluorodeoxyglucose positron emission tomography-computed tomography (FDG-PET/CT): a pilot study." Archives of dermatology **147**(9): 1031-1039.

Miele, L., S. Vallone, et al. (2009). "Prevalence, characteristics and severity of non-alcoholic fatty liver disease in patients with chronic plaque psoriasis." Journal of Hepatology **51**(4): 778-786.

Milosavljevic, J., U. Lindqvist, et al. (2005). "Ultrasound and power Doppler evaluation of the hand and wrist in patients with psoriatic arthritis." Acta radiologica **46**(4): 374-385.

Mogensen, M., J. B. Thomsen, et al. (2007). "Nail thickness measurements using optical coherence tomography and 20-MHz ultrasonography." The British Journal of Dermatology **157**(5): 894-900.

Moll, J. M. and V. Wright (1973). "Psoriatic arthritis." Seminars in Arthritis & Rheumatism **3**(1): 55-78.

Munoz-Fernandez, S., E. de Miguel, et al. (2009). "Enthesis inflammation in recurrent acute anterior uveitis without spondylarthritis." Arthritis & Rheumatism **60**(7): 1985-1990.

Nair, R. P., K. C. Duffin, et al. (2009). "Genome-wide scan reveals association of psoriasis with IL-23 and NF-kappaB pathways." Nature Genetics **41**(2): 199-204.

Nair, R. P., P. E. Stuart, et al. (2006). "Sequence and haplotype analysis supports HLA-C as the psoriasis susceptibility 1 gene." American Journal of Human Genetics **78**(5): 827-851.

Namey, T. C. and L. Rosenthall (1976). "Periarticular uptake of 99mtechnetium diphosphonate in psoriatics: correlation with cutaneous activity." Arthritis & Rheumatism **19**(3): 607-612.

Naredo, E., E. Batlle-Gualda, et al. (2010). "Power Doppler ultrasonography assessment of entheses in spondyloarthropathies: response to therapy of entheseal abnormalities." The Journal of Rheumatology **37**(10): 2110-2117.

Naredo, E., I. Moller, et al. (2008). "Power Doppler ultrasonographic monitoring of response to anti-tumor necrosis factor therapy in patients with rheumatoid arthritis." Arthritis & Rheumatism **58**(8): 2248-2256.

Naredo, E., I. Moller, et al. (2011). "High prevalence of ultrasonographic synovitis and enthesopathy in patients with psoriasis without psoriatic arthritis: a prospective case-control study." Rheumatology **50**(10): 1838-1848.

Narvaez, J., J. A. Narvaez, et al. (2012). "Can Magnetic Resonance Imaging of the Hand and Wrist Differentiate Between Rheumatoid Arthritis and Psoriatic Arthritis in the Early Stages of the Disease?" Seminars in Arthritis & Rheumatism **42**(3): 234-245.

Natarajan, V., A. K. Nath, et al. (2010). "Coexistence of onychomycosis in psoriatic nails: a descriptive study." Indian journal of dermatology, venereology and leprology **76**(6): 723.

Nijsten, T., D. Whalley, et al. (2005). "The psychometric properties of the psoriasis disability index in United States patients." The Journal of Investigative Dermatology **125**(4): 665-672.

Nossent, J. C. and J. T. Gran (2009). "Epidemiological and clinical characteristics of psoriatic arthritis in northern Norway." Scandinavian Journal of Rheumatology **38**(4): 251-255.

Offidani, A., A. Cellini, et al. (1998). "Subclinical joint involvement in psoriasis: magnetic resonance imaging and X-ray findings." Acta Dermato-Venereologica **78**(6): 463-465.

Ohtsuka, T., A. Yamakage, et al. (1994). "Statistical definition of nailfold capillary pattern in patients with psoriasis." International Journal of Dermatology **33**(11): 779-782.

Olivieri, I., L. Barozzi, et al. (1996). "Dactylitis in patients with seronegative spondylarthropathy. Assessment by ultrasonography and magnetic resonance imaging." Arthritis & Rheumatism **39**(9): 1524-1528.

Olivieri, I., S. de Portu, et al. (2008). "The psoriatic arthritis cost evaluation study: A cost-of-illness study on tumour necrosis factor inhibitors in psoriatic arthritis patients with inadequate response to conventional therapy." Rheumatology **47**(11): 1664-1670.

Ortonne, J. P., R. Baran, et al. (2010). "Development and validation of nail psoriasis quality of life scale (NPQ10)." Journal of the European Academy of Dermatology and Venereology : JEADV **24**(1): 22-27.

Ortonne, J. P., C. Paul, et al. (2013). "A 24-week randomized clinical trial investigating the efficacy and safety of two doses of etanercept in nail psoriasis." British Journal of Dermatology **168**(5): 1080-1087.

Ostergaard, M., F. McQueen, et al. (2009). "The OMERACT psoriatic arthritis magnetic resonance imaging scoring system (PsAMRIS): definitions of key pathologies, suggested MRI sequences, and preliminary scoring system for PsA Hands." The Journal of Rheumatology **36**(8): 1816-1824.

Ozcakar, L., A. Cetin, et al. (2005). "Ultrasonographical evaluation of the Achilles' tendon in psoriasis patients." International Journal of Dermatology **44**(11): 930-932.

Ozkan, F., G. Y. Cetin, et al. (2012). "Sonographic evaluation of subclinical entheseal involvement in patients with behcet disease." AJR. American journal of roentgenology **199**(6): W723-729.

Papoutsaki, M., M.-S. Chimenti, et al. (2007). "Adalimumab for severe psoriasis and psoriatic arthritis: an open-label study in 30 patients previously treated with other biologics." Journal of the American Academy of Dermatology **57**(2): 269-275.

Papp, K. A., I. Caro, et al. (2007). "Efalizumab for the treatment of psoriatic arthritis." Journal of Cutaneous Medicine & Surgery **11**(2): 57-66.
Parrish, C. A., J. O. Sobera, et al. (2005). "Modification of the Nail Psoriasis Severity Index." Journal of the American Academy of Dermatology **53**(4): 745-746; author reply 746-747.
Pattison, E., B. J. Harrison, et al. (2008). "Environmental risk factors for the development of psoriatic arthritis: results from a case-control study." Annals of the Rheumatic Diseases **67**(5): 672-676.
Pitarch, G., J. L. Sanchez-Carazo, et al. (2007). "Treatment of psoriasis with adalimumab." Clinical & Experimental Dermatology **32**(1): 18-22.
Pomerantz, R., D. Zell, et al. (2011). "Optical Coherence Tomography Used as a Modality to Delineate Basal Cell Carcinoma prior to Mohs Micrographic Surgery." Case reports in dermatology **3**(3): 212-218.
Punzi, L., M. Pianon, et al. (1998). "Clinical, laboratory and immunogenetic aspects of post-traumatic psoriatic arthritis: a study of 25 patients." Clinical & Experimental Rheumatology **16**(3): 277-281.
Punzi, L., M. Pianon, et al. (1999). "Clinical and laboratory manifestations of elderly onset psoriatic arthritis: a comparison with younger onset disease." Annals of the Rheumatic Diseases **58**(4): 226-229.
Queiro-Silva, R., J. C. Torre-Alonso, et al. (2003). "A polyarticular onset predicts erosive and deforming disease in psoriatic arthritis." Annals of the Rheumatic Diseases **62**(1): 68-70.
Queiro, R., S. Alonso, et al. (2012a). "Entheseal ultrasound abnormalities in patients with SAPHO syndrome." Clin Rheumatol **31**(6): 913-919.
Queiro, R., M. Alperi, et al. (2012b). "Patients with psoriatic arthritis may show differences in their clinical and genetic profiles depending on their age at psoriasis onset." Clinical & Experimental Rheumatology **30**(4): 476-480.
Queiro, R., C. Sarasqueta, et al. (2001). "Comparative analysis of psoriatic spondyloarthropathy between men and women." Rheumatology International **21**(2): 66-68.
Radjenovic, A., B. J. Dall, et al. (2008). "Measurement of pharmacokinetic parameters in histologically graded invasive breast tumours using dynamic contrast-enhanced MRI." The British journal of radiology **81**(962): 120-128.
Radtke, M. A., A. K. Langenbruch, et al. (2011). "Nail psoriasis as a severity indicator: results from the PsoReal study." Patient related outcome measures **2**: 1-6.
Radtke, M. A., K. Reich, et al. (2009). "Prevalence and clinical features of psoriatic arthritis and joint complaints in 2009 patients with psoriasis: results of a German national survey." Journal of the European Academy of Dermatology and Venereology : JEADV **23**(6): 683-691.
Rahman, P., D. D. Gladman, et al. (1998a). "The use of sulfasalazine in psoriatic arthritis: a clinic experience." The Journal of Rheumatology **25**(10): 1957-1961.
Rahman, P., D. D. Gladman, et al. (1998b). "Radiological assessment in psoriatic arthritis." British Journal of Rheumatology **37**(7): 760-765.
Raza, N., A. Hameed, et al. (2008). "Detection of subclinical joint involvement in psoriasis with bone scintigraphy and its response to oral methotrexate." Clinical & Experimental Dermatology **33**(1): 70-73.

Reece, R. J., J. D. Canete, et al. (1999). "Distinct vascular patterns of early synovitis in psoriatic, reactive, and rheumatoid arthritis." Arthritis & Rheumatism **42**(7): 1481-1484.

Reich, K. (2009). "Approach to managing patients with nail psoriasis." Journal of the European Academy of Dermatology and Venereology : JEADV **23 Suppl 1**: 15-21.

Reich, K., K. Kruger, et al. (2009). "Epidemiology and clinical pattern of psoriatic arthritis in Germany: a prospective interdisciplinary epidemiological study of 1511 patients with plaque-type psoriasis." British Journal of Dermatology **160**(5): 1040-1047.

Reich, K., F. O. Nestle, et al. (2005). "Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial." Lancet **366**(9494): 1367-1374.

Reich, K., J. P. Ortonne, et al. (2010). "Skin and nail responses after 1 year of infliximab therapy in patients with moderate-to-severe psoriasis: a retrospective analysis of the EXPRESS Trial." Dermatology **221**(2): 172-178.

Rich, P., C. E. Griffiths, et al. (2008). "Baseline nail disease in patients with moderate to severe psoriasis and response to treatment with infliximab during 1 year." Journal of the American Academy of Dermatology **58**(2): 224-231.

Rich, P. and R. K. Scher (2003). "Nail Psoriasis Severity Index: a useful tool for evaluation of nail psoriasis." Journal of the American Academy of Dermatology **49**(2): 206-212.

Rigopoulos, D., S. Gregoriou, et al. (2010). "Treatment of nail psoriasis with adalimumab: an open label unblinded study." Journal of the European Academy of Dermatology and Venereology : JEADV **24**(5): 530-534.

Rigopoulos, D., S. Gregoriou, et al. (2011). "Efficacy of ustekinumab in nail psoriasis and improvement in nail-associated quality of life in a population treated with ustekinumab for cutaneous psoriasis: an open prospective unblinded study." Dermatology **223**(4): 325-329.

Ritchlin, C. T., A. Kavanaugh, et al. (2009). "Treatment recommendations for psoriatic arthritis." Annals of the Rheumatic Diseases **68**(9): 1387-1394.

Roberts, M. E., V. Wright, et al. (1976). "Psoriatic arthritis. Follow-up study." Annals of the Rheumatic Diseases **35**(3): 206-212.

Robertson, J. C. and M. L. Braune (1974). "Splinter haemorrhages, pitting, and other findings in fingernails of healthy adults." British Medical Journal **4**(5939): 279-281.

Rudwaleit, M., D. van der Heijde, et al. (2011). "The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general." Annals of the Rheumatic Diseases **70**(1): 25-31.

Saad, A. A., D. M. Ashcroft, et al. (2009). "Persistence with anti-tumour necrosis factor therapies in patients with psoriatic arthritis: observational study from the British Society of Rheumatology Biologics Register." Arthritis Res Ther **11**(2): R52.

Sakata, L. M., J. Deleon-Ortega, et al. (2009). "Optical coherence tomography of the retina and optic nerve - a review." Clinical & Experimental Ophthalmology **37**(1): 90-99.

Saleem, B., A. K. Brown, et al. (2009). "Disease remission state in patients treated with the combination of tumor necrosis factor blockade and methotrexate or with disease-modifying antirheumatic drugs: A clinical and imaging comparative study." Arthritis & Rheumatism **60**(7): 1915-1922.

Sattler, E., R. Kaestle, et al. (2012). "Confocal laser scanning microscopy, optical coherence tomography and transonychial water loss for in vivo investigation of nails." British Journal of Dermatology **166**(4): 740-746.

Savnik, A., H. Malmskov, et al. (2002). "MRI of the wrist and finger joints in inflammatory joint diseases at 1-year interval: MRI features to predict bone erosions." European Radiology **12**(5): 1203-1210.

Scarpa, R., F. Ayala, et al. (2006a). "Psoriasis, psoriatic arthritis, or psoriatic disease?" The Journal of Rheumatology **33**(2): 210-212.

Scarpa, R., F. Manguso, et al. (2004). "Is the involvement of the distal interphalangeal joint in psoriatic patients related to nail psoriasis?" Clin Rheumatol **23**(1): 27-30.

Scarpa, R., E. Soscia, et al. (2006b). "Nail and distal interphalangeal joint in psoriatic arthritis." The Journal of Rheumatology **33**(7): 1315-1319.

Schanz, S., J. Henes, et al. (2013). "Magnetic resonance imaging findings in patients with systemic scleroderma and musculoskeletal symptoms." European Radiology **23**(1): 212-221.

Schmitt, J. and D. E. Ford (2010). "Psoriasis is independently associated with psychiatric morbidity and adverse cardiovascular risk factors, but not with cardiovascular events in a population-based sample." Journal of the European Academy of Dermatology and Venereology : JEADV **24**(8): 885-892.

Schoellnast, H., H. A. Deutschmann, et al. (2006). "Psoriatic arthritis and rheumatoid arthritis: findings in contrast-enhanced MRI." AJR. American journal of roentgenology **187**(2): 351-357.

Schraml, C., N. F. Schwenzer, et al. (2011). "Assessment of synovitis in erosive osteoarthritis of the hand using DCE-MRI and comparison with that in its major mimic, the psoriatic arthritis." Academic radiology **18**(7): 804-809.

Schwenzer, N. F., I. Kotter, et al. (2010). "The role of dynamic contrast-enhanced MRI in the differential diagnosis of psoriatic and rheumatoid arthritis." AJR. American journal of roentgenology **194**(3): 715-720.

Setty, A. R., G. Curhan, et al. (2007). "Obesity, waist circumference, weight change, and the risk of psoriasis in women: Nurses' Health Study II." Archives of internal medicine **167**(15): 1670-1675.

Sharp, J. T., G. B. Bluhm, et al. (1985). "Reproducibility of multiple-observer scoring of radiologic abnormalities in the hands and wrists of patients with rheumatoid arthritis." Arthritis & Rheumatism **28**(1): 16-24.

Shbeeb, M., K. M. Uramoto, et al. (2000). "The epidemiology of psoriatic arthritis in Olmsted County, Minnesota, USA, 1982-1991." The Journal of Rheumatology **27**(5): 1247-1250.

Shikiar, R., B. W. Bresnahan, et al. (2003). "Validity and reliability of patient reported outcomes used in psoriasis: results from two randomized clinical trials." Health and quality of life outcomes **1**: 53.

Siannis, F., V. T. Farewell, et al. (2006). "Clinical and radiological damage in psoriatic arthritis." Annals of the Rheumatic Diseases **65**(4): 478-481.

Simon, P., C. Pfoehler, et al. (2012). "Swollen joint count in psoriatic arthritis is associated with progressive radiological damage in hands and feet." Clinical & Experimental Rheumatology **30**(1): 45-50.

Sokoll, K. B. and P. S. Helliwell (2001). "Comparison of disability and quality of life in rheumatoid and psoriatic arthritis." The Journal of Rheumatology **28**(8): 1842-1846.

Soscia, E., R. Scarpa, et al. (2009). "Magnetic resonance imaging of nail unit in psoriatic arthritis." The Journal of rheumatology. Supplement **83**: 42-45.

Spadaro, A., A. Iagnocco, et al. (2011). "Clinical and ultrasonography assessment of peripheral enthesitis in ankylosing spondylitis." Rheumatology **50**(11): 2080-2086.

Stern, R. S., T. Nijsten, et al. (2004). "Psoriasis is common, carries a substantial burden even when not extensive, and is associated with widespread treatment dissatisfaction." The Journal of Investigative Dermatology. Symposium proceedings. **9**(2): 136-139.

Sterry, W., J. P. Ortonne, et al. (2010). "Comparison of two etanercept regimens for treatment of psoriasis and psoriatic arthritis: PRESTA randomised double blind multicentre trial." British Medical Journal **340**: c147.

Stone, M. A., L. M. White, et al. (2009). "Significance of clinical evaluation of the metacarpophalangeal joint in relation to synovial/bone pathology in rheumatoid and psoriatic arthritis detected by magnetic resonance imaging." The Journal of Rheumatology **36**(12): 2751-2757.

Swezey, R. L., D. M. Bjarnason, et al. (1972). "Resorptive arthropathy and the opera-glass hand syndrome." Seminars in Arthritis & Rheumatism **2**(3): 191-244.

Takata, T., Y. Taniguchi, et al. (2011). "(18)FDG PET/CT is a powerful tool for detecting subclinical arthritis in patients with psoriatic arthritis and/or psoriasis vulgaris." Journal of dermatological science **64**(2): 144-147.

Tan, A. L., M. Benjamin, et al. (2007). "The relationship between the extensor tendon enthesis and the nail in distal interphalangeal joint disease in psoriatic arthritis--a high-resolution MRI and histological study." Rheumatology (Oxford) **46**(2): 253-256.

Tan, A. L., A. J. Grainger, et al. (2006a). "A high-resolution magnetic resonance imaging study of distal interphalangeal joint arthropathy in psoriatic arthritis and osteoarthritis: are they the same?" Arthritis & Rheumatism **54**(4): 1328-1333.

Tan, A. L., A. J. Grainger, et al. (2005). "High-resolution magnetic resonance imaging for the assessment of hand osteoarthritis." Arthritis & Rheumatism **52**(8): 2355-2365.

Tan, A. L., S. Tanner, et al. (2013). "High-resolution 18F-fluoride positron emission tomography of distal interphalangeal joint in psoriatic arthritis - a bone-enthesis-nail complex." Rheumatology (Oxford) **52**(5): 898-904.

Tan, A. L., H. Toumi, et al. (2006b). "Combined high-resolution magnetic resonance imaging and histological examination to explore the role of ligaments and tendons in the phenotypic expression of early hand osteoarthritis." Annals of the Rheumatic Diseases **65**(10): 1267-1272.

Tan, Y. M., M. Ostergaard, et al. (2009). "MRI bone oedema scores are higher in the arthritis mutilans form of psoriatic arthritis and correlate with high radiographic scores for joint damage." Arthritis Res Ther **11**(1): R2.

Taylor, W., D. Gladman, et al. (2006). "Classification criteria for psoriatic arthritis: development of new criteria from a large international study." Arthritis & Rheumatism **54**(8): 2665-2673.

Taylor, W. J. and A. A. Harrison (2004a). "Could the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) be a valid measure of disease activity in patients with psoriatic arthritis?" Arthritis & Rheumatism **51**(3): 311-315.

Taylor, W. J., A. Marchesoni, et al. (2004b). "A comparison of the performance characteristics of classification criteria for the diagnosis of psoriatic arthritis." Seminars in Arthritis & Rheumatism **34**(3): 575-584.

Tehranzadeh, J., O. Ashikyan, et al. (2008). "Detailed analysis of contrast-enhanced MRI of hands and wrists in patients with psoriatic arthritis." Skeletal Radiology **37**(5): 433-442.

Teoli, M., A. Zangrilli, et al. (2012). "Evaluation of clinical and ultrasonographic parameters in psoriatic arthritis patients treated with adalimumab: a retrospective study." Clinical & developmental immunology **2012**: 823854.

Tham, S. N., J. J. Lim, et al. (1988). "Clinical observations on nail changes in psoriasis." Annals of the Academy of Medicine, Singapore **17**(4): 482-485.

Tillett, W., L. Costa, et al. (2012a). "The ClASsification for Psoriatic ARthritis (CASPAR) criteria--a retrospective feasibility, sensitivity, and specificity study." The Journal of Rheumatology **39**(1): 154-156.

Tillett, W., G. Shaddick, et al. (2012b). "Joint count reliability in psoriatic arthritis observational trials--an unreported problem." Rheumatology **51**(7): 1333-1334.

Tinazzi, I., S. Adami, et al. (2012). "The early psoriatic arthritis screening questionnaire: a simple and fast method for the identification of arthritis in patients with psoriasis." Rheumatology **51**(11): 2058-2063.

Tinazzi, I., D. McGonagle, et al. (2011). "Preliminary evidence that subclinical enthesopathy may predict psoriatic arthritis in patients with psoriasis." The Journal of Rheumatology **38**(12): 2691-2692.

Torre Alonso, J. C., A. Rodriguez Perez, et al. (1991). "Psoriatic arthritis (PA): a clinical, immunological and radiological study of 180 patients." British Journal of Rheumatology **30**(4): 245-250.

Tosti, A., B. M. Piraccini, et al. (1998). "Calcipotriol ointment in nail psoriasis: a controlled double-blind comparison with betamethasone dipropionate and salicylic acid." British Journal of Dermatology **139**(4): 655-659.

Tosti, A., C. Ricotti, et al. (2009). "Evaluation of the efficacy of acitretin therapy for nail psoriasis." Archives of dermatology **145**(3): 269-271.

Tsai, T. F., T. S. Wang, et al. (2011). "Epidemiology and comorbidities of psoriasis patients in a national database in Taiwan." Journal of dermatological science **63**(1): 40-46.

Van den Bosch, F., B. Manger, et al. (2010). "Effectiveness of adalimumab in treating patients with active psoriatic arthritis (PsA) and predictors

of good clinical responses for arthritis, skin and nail lesions." Annals of the Rheumatic Diseases **69**(2): 394-399.

van der Heijde, D. (2000). "How to read radiographs according to the Sharp/van der Heijde method." The Journal of Rheumatology **27**(1): 261-263.

van der Heijde, D., A. Kavanaugh, et al. (2007). "Infliximab inhibits progression of radiographic damage in patients with active psoriatic arthritis through one year of treatment: Results from the induction and maintenance psoriatic arthritis clinical trial 2." Arthritis & Rheumatism **56**(8): 2698-2707.

van der Heijde, D., J. Sharp, et al. (2005). "Psoriatic arthritis imaging: a review of scoring methods." Annals of the Rheumatic Diseases **64 Suppl 2**: ii61-64.

van Kuijk, A. W., P. Reinders-Blankert, et al. (2006). "Detailed analysis of the cell infiltrate and the expression of mediators of synovial inflammation and joint destruction in the synovium of patients with psoriatic arthritis: implications for treatment." Annals of the Rheumatic Diseases **65**(12): 1551-1557.

Vander Cruyssen, B., F. De Keyser, et al. (2007). "Comparison of different outcome measures for psoriatic arthritis in patients treated with infliximab or placebo." Annals of the Rheumatic Diseases **66**(1): 138-140.

Vasey, F. B. and L. R. Espinoza (1984). Psoriatic arthritis. Spondyloarthropathies. C. A. Orlando, Grune and Stratton**:** 151-185.

Veale, D., S. Rogers, et al. (1994). "Classification of clinical subsets in psoriatic arthritis." British Journal of Rheumatology **33**(2): 133-138.

Veerapen, K. K. (2007). "Pattern of psoriatic arthritis in an Asian population." APLAR Journal of Rheumatology **10**: 287-294.

Wakefield, R. J., P. V. Balint, et al. (2005). "Musculoskeletal ultrasound including definitions for ultrasonographic pathology." The Journal of Rheumatology **32**(12): 2485-2487.

Wakefield, R. J., M. J. Green, et al. (2004). "Should oligoarthritis be reclassified? Ultrasound reveals a high prevalence of subclinical disease." Annals of the Rheumatic Diseases **63**(4): 382-385.

Wallace, A. B. (1951). "The exposure treatment of burns." Lancet **1**(6653): 501-504.

Wassenberg, S., V. Fischer-Kahle, et al. (2001). "A method to score radiographic change in psoriatic arthritis." Zeitschrift fur Rheumatologie **60**(3): 156-166.

Weckbach, S., S. Schewe, et al. (2011). "Whole-body MR imaging in psoriatic arthritis: additional value for therapeutic decision making." European Journal of Radiology **77**(1): 149-155.

Weiner, S. M., S. Jurenz, et al. (2008). "Ultrasonography in the assessment of peripheral joint involvement in psoriatic arthritis : a comparison with radiography, MRI and scintigraphy." Clin Rheumatol **27**(8): 983-989.

Welzel, J., E. Lankenau, et al. (1997). "Optical coherence tomography of the human skin." Journal of the American Academy of Dermatology **37**(6): 958-963.

Wiell, C., M. Szkudlarek, et al. (2007). "Ultrasonography, magnetic resonance imaging, radiography, and clinical assessment of

inflammatory and destructive changes in fingers and toes of patients with psoriatic arthritis." Arthritis Res Ther **9**(6): R119.

Williamson, L., N. Dalbeth, et al. (2004a). "Extended report: nail disease in psoriatic arthritis--clinically important, potentially treatable and often overlooked." Rheumatology **43**(6): 790-794.

Williamson, L., J. L. Dockerty, et al. (2004b). "Clinical assessment of sacroiliitis and HLA-B27 are poor predictors of sacroiliitis diagnosed by magnetic resonance imaging in psoriatic arthritis." Rheumatology **43**(1): 85-88.

Wilson, F. C., M. Icen, et al. (2009a). "Incidence and clinical predictors of psoriatic arthritis in patients with psoriasis: a population-based study." Arthritis & Rheumatism **61**(2): 233-239.

Wilson, F. C., M. Icen, et al. (2009b). "Time trends in epidemiology and characteristics of psoriatic arthritis over 3 decades: a population-based study." The Journal of Rheumatology **36**(2): 361-367.

Wolk, K., L. Mallbris, et al. (2009). "Excessive body weight and smoking associates with a high risk of onset of plaque psoriasis." Acta Dermato-Venereologica **89**(5): 492-497.

Wollina, U., M. Berger, et al. (2001). "Calculation of nail plate and nail matrix parameters by 20 MHz ultrasound in healthy volunteers and patients with skin disease." Skin research and technology : official journal of International Society for Bioengineering and the Skin **7**(1): 60-64.

Wright, V. (1956). "Psoriasis and arthritis." Annals of the Rheumatic Diseases **15**(4): 348-356.

Wright, V. (1961). "Psoriatic arthritis. A comparative radiographic study of rheumatoid arthritis and arthritis associated with psoriasis." Annals of the Rheumatic Diseases **20**: 123-132.

Wright, V. (1978). "Seronegative polyarthritis: a unified concept." Arthritis & Rheumatism **21**(6): 619-633.

Wright, V. and J. M. Moll (1976). Psoriatic Arthritis. Seronegative Polyarthritis. V. Wright and J. M. Moll. Amsterdam, Elsevier North Holland Publishing**:** 169-223.

Wu, Y., D. Mills, et al. (2009). "Impact of psoriasis on patients' work and productivity: a retrospective, matched case-control analysis." American Journal of Clinical Dermatology **10**(6): 407-410.

Zachariae, H. (2003). "Prevalence of joint disease in patients with psoriasis: implications for therapy." American Journal of Clinical Dermatology **4**(7): 441-447.

Zaias, N. (1990). The nail in health and disease, Appleton & Lange.

Zaric, D., O. J. Clemmensen, et al. (1982). "Capillary microscopy of the nail fold in patients with psoriasis and psoriatic arthritis." Dermatologica **164**(1): 10-14.

List of Abbreviations

5TPD	5 Targets PD for Psoriatic Disease
ACPA	Anti-citrullinated Protein Antibody
ACR	American College of Rheumatology
AS	Ankylosing Spondylitis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BASRI	Bath Ankylosing Spondylitis Radiology Index
BML	Bone Marrow Lesion
BMO	Bone Marrow Oedema
BSA	Body Surface Area
BSRBR	British Society for Rheumatology Biologics Register
CASPAR	ClASsification of Psoriatic ARthritis (criteria)
CART	Classification and regression trees
CRP	C Reactive Protein
CT	Computed tomography
DCE	Dynamic Contrast Enhanced (MRI)
DIPJ	Distal Interphalangeal Joint
DLQI	Dermatology Life Quality Index
DMARD	Disease Modifying Anti-Rheumatic Drug
EARP	Early ARthritis for Psoriatic patients questionnaire
ESR	Erythrocyte Sedimentation Ratio
EULAR	European League Against Rheumatism

GRAPPA	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
GS	Gray Scale
GUESS	Glasgow Ultrasound Enthesitis Scoring System
GWAS	Genome Wide Association Study
HAQ	Health Assessment Questionnaire
HC	Healthy Controls
HLA	Human Leukocyte Antigen
ICC	Intraclass Correlation Coefficient
IPJ	Interphalangeal Joint
IRE	Initial Rate of Enhancement
JSN	Joint Space Narrowing
LDI	Leeds Dactylitis Index
LEI	Leeds Enthesitis Index
MASES	Maastricht Ankylosing Spondylitis Enthesitis Score
MCP	Metacarpophalangeal (joint)
ME	Maximal Enhancement
MEI	Mander Enthesitis Index
MHC	Major Histocompatibility Complex
mNAPSI	modified Nail Psoriasis Severity Index
MRI	Magnetic Resonance Imaging
mSASSS	modified Stoke Ankylosing Spondylitis Spine Score
MTP	Metatarsophalangeal (joint)
MTX	Methotrexate
NAPSI	Nail Psoriasis Severity Index
NICE	National Institute for health and Care Excellence
NPQ10	Nail Psoriasis Quality of life scale

NSAID	Non-steroidal Anti-inflammatory Drug
NVRI	Nailfold Vessel Resistance Index
OA	Osteoarthritis
OCT	Optical Coherence Tomography
OMERACT	Outcome Measures in Rheumatoid Arthritis Clinical Trials
PABAK	Prevalence-adjusted, bias-adjusted Kappa
PAQ	Psoriatic and Arthritic Questionnaire
PASE	Psoriatic Arthritis Screening and Evaluation tool
PASI	Psoriasis Area and Severity Index
PD	Power Doppler
PDI	Psoriasis Disability Index
PEST	Psoriasis Epidemiology Screening Tool
PET	Positron Emission Tomography
PIP	Proximal Interphalangeal (joint)
PNSS	Psoriasis Nail Severity Score
PsA	Psoriatic Arthritis
PsAMRIS	Psoriatic Arthritis Magnetic Resonance Imaging Scoring system
PsARC	Psoriatic Arthritis Response Criteria
PUVA	Psoralen plus UVA light phototherapy
RA	Rheumatoid Arthritis
RAMRIS	Rheumatoid Arthritis Magnetic Resonance Imaging Scoring
RCT	Randomised Controlled Trial
ROC	Receiver Operating Curves
ROI	Region Of Interest
RR	Relative Risk
SAPHO	Synovitis, Acne, Pustulosis, HyperOstosis

SD	Standard Deviation
SEI	Sonographic Enthesitis Index
SJC	Swollen Joint Count
SpA	Spondyloarthropathy
SPARCC	Spondyloarthritis Research Consortium of Canada (Enthesitis Index)
SSATG	South Swedish Arthritis Treatment Group
ToPAS	Toronto Psoriatic Arthritis Screen
TJC	Tender Joint Count
TNF	Tumour Necrosis Factor
US	Ultrasound
VAS	Visual Analogue Scale